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Improving clinical outcomes in rheumatoid arthritis a patient centred approach

Pollard, Louise

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**IMPROVING CLINICAL OUTCOMES IN RHEUMATOID ARTHRITIS:
A PATIENT CENTRED APPROACH**

LOUISE CATHERINE POLLARD

**SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY**

ABSTRACT

The existing medical model for managing rheumatoid arthritis (RA) focuses on minimising joint inflammation using suppressive treatments. However, patients have broader concerns spanning other symptoms like fatigue and pain and the way their health care is delivered. This thesis used qualitative and quantitative research methods to address three inter-related aspects of clinical care. Firstly, identifying critical challenges for providing patient-centred care. Secondly, defining outcomes important to patients like fatigue and pain and concomitant fibromyalgia. Finally, examining temporal changes in the RA management and evaluating aspects of clinical decision making.

Firstly the thesis shows current care is not optimal. Key limitations include: being insufficiently patient-centred, failing to integrate management across the primary/secondary divide, over-emphasising drug treatment and overlooking "whole-person" care.

Secondly, care overlooks several crucially important areas to RA patients. Many patients had high levels of fatigue, associated with pain, disability and psychological factors. Their fatigue spanned several domains. Current fatigue questionnaires are heavily weighted towards psychological aspects, and a more balanced assessment is needed. Pain, a dominant RA symptom, is often not directly addressed. The research showed central sensitisation causes persistent pain in many RA patients; it may require different management approaches. The research also characterised patients with the fibromyalgic rheumatoid clinical phenotypes; their higher disease activity scores may not fully reflect disease activity. Despite changes in treatment over the years their disease activity scores have not improved significantly, unlike RA patients in general. Different treatment strategies are needed to improve their outcomes.

Finally although patients with high disease activity usually have their treatment changed when reviewed in rheumatology clinics, patients with moderate disease activity often have insufficient treatment changes; patients' age has a significant influence on treatment decisions. Strategies are needed to better target moderate disease activity and overcome the limiting effect of age on treatment decisions.

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LIST OF ABBREVIATIONS

Activities of living (ADL)
 American college of rheumatology (ACR)
 Amyloid a (AA)
 Anti-citrullinated protein antibody (ACPA)
 Anti-cyclic citrullinated peptide (anti-CCP)
 Antigen presenting cells (APCs)
 Arthritis and musculoskeletal alliance (ARMA)
 Arthritis impact measurement score (AIMS)
 British society of rheumatology (BSR)
 Clinical disease activity index (CDAI)
 Cognitive behavioural therapy (CBT)
 C-reactive protein (CRP)
 Cyclo-oxygenase (COX)
 Disease activity score (DAS)
 Disease activity score for twenty-eight joints (DAS28)
 Disease modifying anti-rheumatic drug (DMARD)
 Distal interphalangeal (DIP)
 Early morning stiffness (EMS)
 Early rheumatoid arthritis network (ERAN)
 Erythrocyte sedimentation rate (ESR)
 European league against rheumatism (EULAR)
 Euroqol (EQ-5d)
 Functional assessment of chronic illness therapy –fatigue scale (FACIT-F)
 GP with a specialist interest (GPSI)
 Health assessment questionnaire (HAQ)
 Hospital anxiety and depression scale (HADS)
 Human α -fetoprotein (AFP)
 Human leukocyte antigen (HLA)
 Hypothalamic-pituitary-adrenal (HPA)
 Interferon gamma (IFN γ)
 Interleukin (IL)
 International classification of disease (ICD)

Interstitial lung disease (ILD)
Magnetic resonance imaging (MRI)
Medication adherence rating scale (MARS)
Metacarpophalangeal (MCP)
Metatarsophalangeal (MTP)
Modified HAQ (mHAQ)
Multidimensional assessment of fatigue (MAF)
Multidimensional fatigue symptom inventory (MFSI)
Multidimensional HAQ (mdHAQ)
National audit office (NAO)
National institute for health and clinical excellence (NICE)
National rheumatoid arthritis society (NRAS)
Non steroidal anti-inflammatory drugs (NSAIDs)
Nottingham health profile (NHP)
Occupational therapists (OTs)
Oral contraceptive pill (OCP)
Outcome measures in rheumatoid arthritis clinical trials (OMERACT)
Overall status in RA (OSRA)
Patient global assessment (PGA)
Physician global assessment (PhysGA)
Primary care trust (PCT)
Proximal interphalangeal (PIP)
Quality and outcomes framework (QOF)
Quality of well being scale (QWB scale)
Rheumatoid arthritis impact of disease (RAID)
Randomised controlled trial (RCT)
Receiver operator characteristic (ROC)
Receptor activator of nuclear factor kappa b (RANK)
Rheumatoid arthritis (RA)
Rheumatoid arthritis pain scale (RAPS)
Ritchie articular index (RAI)
Short form 36 (SF-36)
Simple disease activity index (SDAI)

Standard gamble (SG)

Standardised mortality rate (SMR)

Statistical package for the social sciences (SPSS)

Swollen joint count (SJC)

Systemic lupus erythematosus (SLE)

Tender joint count (TJC)

Time trade off (TTO)

Total quality management (TQM)

Tuberculosis (TB)

Tumour necrosis factor (TNF)

Ultrasound (US)

Verbal rating scale (VRS)

Visual analogue scale (VAS)

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PUBLICATIONS

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Pollard LC, Scott DL. Evidence in favour of fibromyalgic rheumatoid arthritis: High trigger point counts and fatigue scores indicate a different clinical phenotype. Rheumatology 2007; 46 (Suppl 1): I99.

Pollard LC, Morrison C, Scott DL. ARMA standards of care audit for patients with inflammatory arthritis: Opportunities for better care. Rheumatology 2008; 47 (Suppl 2): II117.

Pollard L, Scott IC, Kiely P, Williams R, Walsh D, Scott DL, Young A. Assessing health status in early rheumatoid arthritis (RA) using SF-36 to identify unexplored treatment needs. Rheumatology 2008; 47 (Suppl 2): II33

Pollard L, Khoshaba B, Kingsley GH, Choy EH, Scott DL. Nottingham health profile (NHP) and responses to disease modifying drugs (DMARDs), steroids and TNF inhibitors in active rheumatoid arthritis. Rheumatology 2008; 47 (Suppl 2): II44.

Pollard LC, Scott DL, Choy EH. Evidence for chronic pain in rheumatoid arthritis (RA) resulting in central sensitisation. Rheumatology 2008; 47 (Suppl 2): II8.

Pollard LC, Scott DL, Donaldson N, Choy EH. Fatigue is an independent driver of disability in rheumatoid arthritis. Arthritis Rheum 2008; 58 (Suppl): S278-S279

Graves H, **Pollard LC**, Lempp H, Kingsley GH, Scott DL. Perceived Barriers To Integrated Care In Rheumatoid Arthritis (RA): Views Of Providers And Recipients Of Primary And Secondary Care Services. Rheumatology 2009; 48 (Suppl 1): I107.

Pollard LC, Scott DL, Donaldson N, Choy E. Fatigue is an independent driver of disability in rheumatoid arthritis. *Rheumatology* 2009; 48 (Suppl 1): I131-I132

Ma MH, **Pollard LC**, Kingsley GH, Scott DL. Rheumatoid arthritis (RA): the assessment of disease activity in clinical practice. Does it influence treatment decisions? *Rheumatology* 2009; 48 (Suppl 1): I134-I134.

Pollard LC, Scott DL, Donaldson N, Choy EH. Fatigue in rheumatoid arthritis, what are we measuring? A factor analysis of fatigue instruments. *Rheumatology* 2009; 48 (Suppl 1): I135

Ma MH, Ibrahim F, **Pollard L**, Fekete Z, Kingsley GH, Scott DL. Treatment decisions in rheumatoid arthritis: do we undertreat the elderly population? *Rheumatology* 2010; 49 (Suppl 1); I23.

FULL PAPERS

Pollard L, Choy EH, Scott DL. The consequences of rheumatoid arthritis: quality of life measures in the individual patient. *Clin Exp Rheumatol* 2005; 23(5 Suppl 39): S43-52.

Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology* 2006; 45: 885-9.

Pollard LC, Kingsley GH, Choy EH, Scott DL. Fibromyalgic rheumatoid arthritis and disease assessment. *Rheumatology* 2010; 9: 24-8.

Pollard LC, Graves H, Scott DL, Kingsley GH, Lempp H. Perceived barriers to integrated care in rheumatoid arthritis: views of recipients and providers of care in an inner-city setting. *BMC Musculoskelet Disord* 2011; 12: 19.

Pollard LC, Ibrahim F, Choy EH, Scott DL. Pain thresholds in rheumatoid arthritis: the effect of tender point counts and disease duration. *J Rheumatol* 2012; 39: 28-31.

CHAPTER 1. INTRODUCTION

1.1. AN OVERVIEW OF RHEUMATOID ARTHRITIS

1.1.1. History

Rheumatoid arthritis (RA) is one of the most common types of chronic polyarthritis affecting approximately 1% of the world population [Gibofsky A. 2012] and it leads to significant disability through a combination of synovitis, pain and fatigue. RA can affect both sexes but is more common in females and has a peak onset during the fifth decade of life. Although research has given us a clearer understanding of the inflammatory pathways which are involved in the pathogenesis of RA [Choy et al., 2001], there is still no cure and therefore treatment is aimed at reducing inflammation, improving symptoms and ultimately reducing disability and improving quality of life for these patients.

The first recognised description of rheumatoid arthritis was in 1800 by the French physician Landré-Beauvais (1772-1840). This was part of his doctoral thesis, although at the time he recognised it as distinct from previously described gout, he termed the ‘new’ disease asthenic gout. Landre-Beauvais studied nine patients at Salpêtrière hospital in Paris and described permanent swelling of the joints and deformities and after several years some patients became severely disabled. Post mortem examinations showed abnormally thickened tissue in the joints as well as the surface of joints showing swelling, ulcers and ‘invasion by flesh’. [Landr -Beauvais 2001]

Although RA may be thought of as a modern disease, the earliest appearance of RA was noted in remains of Indian skeletons dating from 4500 BC found in what is now known as Tennessee [Uhl g 2011]. It has also been suggested the in RA may have evolved from ankylosing spondylitis based on remains found in Sicily dating back to the Hellenistic period (330-210 B.C.) [Kelpinger 1978]

The term rheumatoid arthritis was first coined by Sir Alfred Garrod in 1859 and he was the first person to distinguish it from gout [Storey 2001]. RA as a term was adopted officially in 1922 by the Empire Rheumatism Council and in 1941 by the American Rheumatism Association.

1.1.2. Diagnostic Criteria

There is no single laboratory test or sign which will diagnose RA. The diagnosis relies on a thorough history and examination in combination with laboratory and radiological findings. Until recently the most widely used criteria used to differentiate RA from other inflammatory arthritides were the 1987 American College of Rheumatology (ACR) diagnostic criteria. [Arnett et al. 1988] (Table 1.1) These have recently been updated to allow earlier diagnosis of disease and include the anti-cyclic citrullinated peptide (anti-CCP) antibody [Aletaha et al. 2010]. (Table 1.2)

Table 1:1 1987 ACR Criteria for the Classification of Rheumatoid Arthritis

Criterion	Definition
1. Morning Stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks.

Table 1:2 2010 ACR/EULAR Classification Criteria For Rheumatoid Arthritis

Target population (Who should be tested?): Patients who:	
1) have at least 1 joint with definite clinical synovitis (swelling)	
2) with the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of $\geq 6/10$ is needed for classification of a patient as having definite RA)	
A. Joint involvement	
1 large joint	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF <i>and</i> negative ACPA	0
Low-positive RF <i>or</i> low-positive ACPA	2
High-positive RF <i>or</i> high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP <i>and</i> normal ESR	0
Abnormal CRP <i>or</i> abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥ 6 weeks	1

ACPA = anti-citrullinated protein antibody.

Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

“Large joints” refers to shoulders, elbows, hips, knees, and ankles.

“Small joints” refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

1.1.3. Epidemiology

RA is estimated to affect approximately 1% of the UK population [Symmonds et al. 2002]. Its annual incidence is 1-5 per 10,000 per population. The incidence and prevalence of RA may have decreased in recent years; several factors have been implicated. A study published in 2002 by Symmonds et al, looking at the prevalence of RA in the UK based on the 1987 ACR criteria; showed a fall in incidence since the 1960s. This fall may have been related to the protective effect of the oral contraceptive pill (OCP) or other factors related to OCP use. They found no fall in women aged 75 and over, who would not have had the OCP available to them; there was little evidence of a fall in prevalence in men.

In 2009 the national audit office estimated that in England some 580,000 adults have RA, with around 26,000 new diagnoses each year. They also estimated that RA costs the NHS around £560 million a year in healthcare costs, with the majority of this in the acute sector, and that the additional cost to the economy of sick leave and work-related disability is £1.8 billion a year. [National Audit Office 2009] The economic burden of RA is high in other Western societies as well, including Canada and the United States of America (USA). [Zhang et al. 2011] Whilst RA is fairly common in northern Europe and North America, in other parts of the developing world such as rural West Africa it appears rare. [Ouédraogo 2011] These variations may be indicative of different genetic risks and environmental exposures

Alamanos et al [2006] systematically reviewed incidence and prevalence studies of RA based on the 1987 revised ACR criteria. They identified 28 relevant studies. Nine were incidence studies, 17 were prevalence studies and 2 estimated both prevalence and incidence rates. They found a significant difference of prevalence estimates between northern European and American countries and developing countries. South European countries had lower incidence rates than North American and north European countries. They concluded that the occurrence of RA varies among countries and areas of the world. Although a decreasing trend was observed in countries with high rates of RA incidence and prevalence, the relatively small number of studies for most areas of the world and the lack of incidence studies for the developing countries limits the understanding of worldwide RA. The difference

between the incidence and prevalence rates are summarised in Tables 1.3 and 1.4.
[Alamanos et al. 2006]

Table 1:3 Incidence Studies of Rheumatoid Arthritis

Publication	Year	Country	Study Type	Incidence (cases/10 ³ inhabitants)			Population Age (y)
				<i>Total</i>	<i>Male</i>	<i>Female</i>	
Doran	2002	USA	Retrospective	0.5	0.3	0.6	≥18
Savolainen	2003	Finland	Prospective	0.4	0.3	0.5	≥16
Chan	1993	USA	Retrospective	0.3	0.2	0.5	≥18
Kaipiainen-Seppanen	2000	Finland	Retrospective	0.3	0.2	0.4	≥16
Riise	2000	Norway	Retrospective	0.3	0.2	0.4	≥20
Uhlig	1998	Norway	Retrospective	0.3	0.1	0.4	20–79
Kaipiainen-Seppanen	2001	Finland	Retrospective	0.3	0.2	0.4	≥16
Drosos	1997	Greece	Retrospective	0.2	0.1	0.4	≥16
Symmons	1994	England	Prospective	0.2	0.1	0.3	≥16
Soderlin	2002	Sweden	Prospective	0.2	0.2	0.3	≥16
Guillemin	1994	France	Retrospective	0.1	0.1	0.1	20–70

Table 1:4 Prevalence Studies Of Rheumatoid Arthritis

Publication	Year	Country	Study Type	Prevalence (cases/10 ³ inhabitants)			Population Age (y)
				<i>Total</i>	<i>Male</i>	<i>Female</i>	
Gabriel	1999	USA	Retrospective	10.7	7.4	13.7	≥35
Symmons	2002	England	Cross-sectional	8.5	4.4	11.2	≥16
Hakala	1993	Finland	Retrospective	8.0	6.1	10.0	≥16
Andrianako	2003	Greece	Cross-sectional	7		19	
Simmonson	1999	Sweden	Cross-sectional	5.1		20–74	
Saraux	1999	France	Cross-sectional	5.0	2.4	7.6	≥18
Carmona	2002	Spain	Cross-sectional	5	2	8	≥20
Power	1999	Ireland	Cross-sectional	5			
Akar	2004	Turkey	Cross-sectional	3.6	1.5	7.7	≥20
Kvien	1997	Norway	Cross-sectional	4.4	1.9	6.7	20–79
Riise	2000	Norway	Retrospective	4.3	2.7	5.8	≥20
Pountain	1991	Oman	Cross-sectional	3.6	16		
Drosos	1997	Greece	Retrospective	3.5	1.9	4.5	≥16
Lau	1993	China	Cross-sectional	3.5			≥16
Cimmino	1998	Italy	Cross-sectional	3.3	1.3	5.1	≥16
Guillemin	2005	France	Cross-sectional	3.1	0.9	5.1	≥18
Dai	2003	China	Cross-sectional	2.8	1.4	4.1	≥16
Spindler	2002	Argentina	Retrospective	2.0	0.6	3.2	≥16
Stojacovic	1998	Yugoslav	Cross-sectional	1.8	0.9	2.9	≥20

1.1.4. Pathogenesis

The prime target for inflammation in RA is the synovium, which when inflamed is termed synovitis. The synovium in a normal joint serves as an important source of nutrients for cartilage as cartilage itself has no blood supply. Another important function of the synovium is the production of hyaluronic acid, which acts as lubrication for the joint. Hyaluronic acid is present in small volumes in the normal joint and helps normal movement and function. The synovial cells also produce collagens and fibronectins which make up the structural framework of the synovial interstitium. In RA, the inflamed synovium produces larger quantities of synovial fluid, which clinically is seen as joint swelling or effusion and is one of the hallmarks of RA. The fluid is also less viscous than normal synovial fluid and contains high levels of inflammatory cells and other mediators of the inflammatory process.

The lining of normal synovium is only a few cells thick (1-3), with few if any inflammatory cells, but in RA the lining becomes markedly hypertrophied, up to 8-10 cells thick. Cells seen in the layer in RA are predominantly macrophages and fibroblasts. The layer below this, the subintimal layer, contains the blood vessels which supply the synovium and normally contains very few cells. However, in RA, this layer is heavily infiltrated with inflammatory cells, including T cells, B cells and macrophages. Accompanying this heavy infiltration is new blood vessel formation, called angiogenesis. The greatly hypertrophied synovium is also called pannus and it has almost tumour like qualities as it invades and erodes adjacent cartilage and bone, which leads to the erosions seen on x-ray.

It is felt that T cells play a central role in the pathogenesis of RA, but other cells such as B cells, macrophages, fibroblasts and osteoclasts also play vital roles in the inflammatory process. [Choy et al. 2001] The first step in the inflammatory process in RA is the uptake of antigen by antigen presenting cells (APCs), which is then degraded into peptides which are inserted into the groove of HLA-DR molecules on the surface of the APCs and presented to CD4+ T cells. The antigens which trigger this process are unknown; they may be autoantigens, microbial antigens or other external antigens. The T cell receptor recognises the HLA-DR, antigenic peptide complex and through a series of molecular events and gene transcription the T cell

becomes activated. [Goronzy et al. 1993] In order for the T cell to become fully activated several co-stimulation signals are also required. Without this second signal the T cell fails to activate and become anergic. This co-stimulation pathway has become the target of new therapy for RA. [Fiocco et al. 2008]

After activation of the T cell, there is release of a number of proinflammatory cytokines. Interleukin-2 (IL-2) is released, which is a growth factor for T cells and leads to their clonal expansion. T cells also release a number of other mediators, some of the most important being interferon gamma (IFN γ) and IL-17. IL-17 activates osteoclasts which in turn erode bone and IFN γ activates macrophages which release chemokines and inflammatory cytokines including IL-1 and tumour necrosis factor alpha (TNF α), which have also become targets for therapy in RA. The inflammatory cytokines also work on synovial fibroblasts and or synoviocytes to activate them and the chemokines are responsible for the migration of monocytes, neutrophils, T and B cells into the synovium. [Choy 2012]

In addition to releasing proinflammatory cytokines the T cell can also interact directly with macrophages, synovial fibroblasts and osteoclasts. T cells can directly activate osteoclasts via cell to cell interaction. Activated T cells within the RA synovium possess a ligand called receptor activator of nuclear factor κ B (RANK) ligand. Non activated T cells do not express RANK ligand. Osteoclast precursors express a receptor for RANK ligand on their surface. When RANK ligand on an activated T cell interacts with the RANK receptor on the osteoclast precursors, a series of molecular events leads to the differentiation of the precursors into osteoclasts, as well as their activation and survival and thus bone resorption. [Shiozawa et al. 2011]

The role of B cells in the pathogenesis of RA has come to the fore with the successful treatment of RA patients with anti B cell therapy [Edwards et al. 2001]. The B cell has several possible roles in the inflammatory pathway in RA. B cells can act as antigen presenting cells to T cells and also as a co-stimulatory signal for T cell expansion. B cells themselves are also capable of secreting proinflammatory cytokines such as TNF α . B cells also produce rheumatoid factor and other

autoantibodies, which can produce immune complexes and fix complement leading to inflammation.

1.1.5. Outcome Predictors

1.1.5.1. Genetics

RA is a complex disease and is often heterogeneous in its clinical presentation. This heterogeneity can continue throughout the course of disease with variable disease progression, severity and response to treatment. This variability between individuals is likely secondary to genetic factors.

The role of HLA DRB1 genes has been known for many years. The first clue that T cells may be an important driver of inflammation in RA came with the discovery of the link between RA and HLA-DR4/DR1 [Winchester 1981]. The only known function of DR molecules is to present antigen to T cells.

Several different HLA DRB1 alleles have been shown to be associated with RA and some alleles have much stronger associations than others; HLA DRB1*0404 is a much stronger susceptibility factor than HLA DRB1*0401. [Weyand et al. 1992] In contrast some HLA DRB1 alleles may actually be protective. Recent thinking suggests that the association between HLA DRB1 and RA is related to severity of disease rather than risk of development of disease. [Toda et al. 1994] Twin studies have shown that RA has a heritability of approximately 60%. [MacGregor et al. 2000]

1.1.5.2. Sex and Hormonal Factors

RA affects almost three times as many females as males. Therefore a lot of research has focused on examining the role of hormonal and reproductive factors in the development and risk of RA. Interestingly testosterone levels are lower in men who have RA. [Spector et al. 1988] However, there are no differences in levels of sex hormones in females with RA compared to unaffected females. [Heikkila et al. 1998] There is some evidence that exogenous hormones exert some effect. It was initially felt that the oral contraceptive pill reduced the risk of developing RA, but a subsequent study found that the protective effect was lost over time, thus, although

the oral contraceptive pill does not reduce the overall risk, it does appear to delay the onset of RA. [Hannafor et al. 1990]

Studies looking at the influence of pregnancy have produced conflicting results. With some studies suggesting that women who have had no children are at greater risk of developing RA, with other studies showing there to be no increased risk in single women. [Spector et al. 1989] Although it is well accepted that RA tends to remit during pregnancy, the mechanisms have not been established. [Ostensen et al. 2002] Symptomatic relief becomes more pronounced as the pregnancy progresses, with more patients achieving remission by the third trimester. [Da Silva et al. 1992] This remission coincides with the increase in maternal and fetal levels of human α -fetoprotein (AFP), which has immunomodulatory properties; [Irony-Tur-Sinai et al. 2006; Hooper et al. 1989] hence; it may be a significant contributory factor. AFP is produced at low levels throughout life; however, the fetus produces much higher levels of AFP. During pregnancy, AFP reaches maximal concentrations during the third trimester. After delivery, levels of AFP fall to normal levels. [Pollard et al. 2007]

The postpartum period appears to be a high risk time for development of disease, particularly after a first pregnancy. Some of this risk is now felt to be due to breastfeeding and those females who breastfeed after their first pregnancy have the highest risk of developing RA. It has been postulated that this may be due to exposure to prolactin which has proinflammatory properties. [Silman et al. 1994]

1.1.5.3. Infection

For many years there has been a widely felt belief that RA is triggered by an infection. Although a substantial number of people develop RA within a few weeks of an infection, numerous studies have failed to identify a specific causal antigen.

1.1.6. Clinical Features

Most cases of RA develop insidiously over a few weeks to months. Patients often initially notice stiffness in the joints with associated pain on movement and tenderness to palpation of the affected joints. Although a few joints may be affected

at onset, the disease is usually polyarticular and there is usually a sequential addition of involved joints. The small joints of the hands (metacarpophalangeal, proximal interphalangeal and wrist joints) and feet (metatarsophalangeal joints) are invariably involved, usually at an early stage. However, a smaller number of patients may present with a large joint onset of disease, in those that have a monoarticular onset, the knee is the most commonly affected joint. Occasionally patients have an acute or ‘explosive’ onset of symptoms over 24 to 48 hours. [Hart 1997]

The stiffness associated with RA is characteristically worse in the mornings and lasts usually more than an hour but can last for several hours and its duration can be a useful gauge of disease activity. [Sierakowski et al. 2011] Although the stiffness in RA is most common in the morning, stiffness also commonly develops in the evenings and after long periods of inactivity, often referred to as ‘gelling’. This is in contrast to patients with degenerative arthritis who also have stiffness with inactivity but this usually only lasts for a few minutes.

1.1.6.1. Clinical Presentation and Subtypes

RA has heterogeneous clinical features and although it usually presents with polyarticular or monoarticular arthritis, there are a number of other clinical subtypes that are well recognised. [Scott et al. 2007] These include palindromic and polymyalgic onset RA. Palindromic RA is characterised by transient synovitis that can affect different joints. The transient synovitis can last anywhere between a few hours to a few days and then completely resolve. Between episodes the joints often feel normal. The time between episodes is very variable. A significant number of people with palindromic RA will develop into classical RA. In polymyalgic onset RA, patients often develop symptoms very similar to polymyalgia rheumatica with muscle pain and prolonged stiffness in predominantly the shoulder girdle but also the pelvic girdle.

Another evolving clinical subtype is fibromyalgic rheumatoid. This has been partially defined by Wolfe and colleagues in RA on the basis of high levels of pain, fatigue and disability without significant synovial inflammation. [Wolfe et al. 2004]

It is worthwhile identifying this subtype, which resembles fibromyalgia seen in the general population, because it may respond to different therapeutic approaches.

1.1.6.2. Disease Course

Disease expression is variable but the majority of patients have a gradually progressive course of disease with joint damage and deformity leading to disability. A proportion of patients will have a fairly mild course of disease with little impairment. The extent of disability is often determined within the first few years of disease, with gradual worsening of the level of functioning thereafter. [Masi 1983; Morel et al. 2005] This confirms the need to treat disease early and aggressively in order to prevent disability.

1.1.6.3. Joint Involvement

Chronic synovitis leads to progressive joint damage. Pannus formation erodes into adjacent cartilage and bone. Joint involvement in RA is characteristically symmetrical and commonly affects the MCPs, PIPs, wrists, elbows, shoulders, knees and MTPs. Early in the disease process swelling in these joints may be apparent and chronic inflammation leads to joint destruction and the typical joint deformity which is characteristic of RA.

The typical deformities include ulnar deviation at the MCPs and swan neck deformities of the digits, which is defined as hyperextension at the PIP joints and flexion at the distal interphalangeal (DIP) joints. These deformities are a consequence of joint swelling and also associated tenosynovitis. In early disease these deformities may be correctable; however, later in disease other deformities of the hands such as boutonnière's may develop which impact on the functioning of the hand. Boutonnière deformities are defined as hyperextension at the MCP joints, flexion at the PIP joints and hyperextension at the DIP joints. The thumb deformity associated with RA is the so called Z deformity, which is flexion at the MCP and hyperextension at the interphalangeal joint.

1.1.6.4. Systemic Involvement

RA is a chronic inflammatory arthritis and most commonly affects the joints, however, RA can be a systemic disease and severe arthritis shortens life expectancy by 6-10 years, equivalent to the impact of diabetes, Hodgkin's disease, and triple vessel coronary artery disease. [Rasker et al. 1981]

Systemic or extra-articular manifestations of RA are present in approximately 8-12% of patients and there is evidence that those patients with systemic manifestations have increased morbidity and mortality compared to those with no extra articular features. [Turesson et al. 1999] The extra-articular manifestations are often associated with high levels of disease activity, high inflammatory markers and high levels of rheumatoid factor. These patients are known to have a poor prognosis and therefore early aggressive therapy should be instituted to lower the risk of systemic manifestations and reduce morbidity and mortality. [Turesson et al. 2002]

Constitutional features include fatigue, fever, anorexia and weight loss. Many of the systemic features are driven by IL-6; it activates the hypothalamic-pituitary-adrenal (HPA) axis to produce fever, stimulates haematopoiesis, including stimulating megakaryocyte progenitors which cause an increase in platelets, activating hepatocytes to produce the acute phase reactants CRP and amyloid A, as well as stimulating the activation of osteoclasts which have as major role in osteoporosis. [Hashizume et al. 2011] Extra-articular manifestations in RA can affect almost any system in the body, although the most commonly affected are the skin (rheumatoid nodules, eyes and mouth (secondary Sjögren's) and lungs (pulmonary fibrosis). [Turesson et al. 2003]

1.1.7. Impact of Rheumatoid Arthritis on Society and the Individual

The impact of RA on the individual can be obvious in those with observable disability and deformities from longstanding inflammation. However, other forms of disability are less obvious such as the impact of chronic disease on mental health and the often accompanying chronic pain. RA itself is a significant cause of morbidity

and mortality and is said to reduce life expectancy by up to five years. [Wolfe et al. 1994]

The cost of RA to the individual and society can be thought of in terms of ‘direct’ and ‘indirect’ costs. The ‘direct’ costs are fairly easily measurable in terms of costs of hospital appointments with specialists and allied health care professionals, drug treatments, drug monitoring, investigations and hospital admissions. The ‘indirect’ costs are less easily measurable and include less tangible costs such as loss of productivity, loss of work time, incapacity and disability benefits as well as the impact on family with many relatives often acting as unpaid carers.

Patients with RA often leave full time employment early in disease and a proportion will never return to full time work. Those who do work often need considerable time off for repeated hospital appointments, monitoring of the possible side effects associated with treatment and sessions with allied health care professionals such as physiotherapists and occupational therapists. Numerous tools have been designed to measure outcomes in RA patients with regards to disease activity, overall health and disability; however, tools which attach a monetary value have been attempted but have been less successful.

1.1.7.1. Disability

Historically, the impact of chronic diseases including RA on patients’ lives has been defined in terms of three different levels defined by the World Health Organization: impairment, disability and handicap. In essence impairment is a loss of anatomical or psychological function, disability is an inability to perform normal activities due to impairment and handicap is the disadvantage for an individual resulting from an impairment or disability that limits the fulfilment of a normal role in life. This overarching concept is now being superseded by the International Classification of Functioning, Disability and Health (the ICF framework). This latter approach classifies patients’ problems into four different components, which can be used to generate an individual code that is akin to that generated by the international classification of disease (ICD-10). These four components comprise body functions and structures (similar to the previous concept of impairment), activities and

participation (similar to the previous concepts of disability and handicap), environmental factors, and personal factors. The first two components define functioning and disability, whilst the second two are regarded as contextual factors.

1.1.7.2. Work Disability

Approximately half of RA patients in the UK are of working age at the onset of symptoms. [Symmons et al. 1994] A study from the US suggests that the greatest risk of work disability seems to occur within the first three years following the onset of symptoms. [Sokka 2003] One longitudinal study of patients with early RA in the UK has shown that just over a fifth of patients who were in employment at the onset of symptoms of RA stopped working after 5 years of disease onset because of their RA. [Young et al. 2002] A study from Canada showed that about a third of RA patients from their cohort of 239 patients left employment early, although this was influenced by socioeconomic factors. [Backman et al. 2004]

Work related disability is particularly common for RA, with around 9.4 million working days lost in the UK due to RA in 1999-2000, equivalent to £833 million in lost production. [ARMA standards of care for people with inflammatory arthritis 2004] This is clearly a significant sum of money, especially considering the current economic situation. In recent years there has been more focus on the cost of RA work disability, predominantly spearheaded by the drug companies responsible for the development of biologic therapies who are understandably eager to show that their treatments are cost beneficial given their relatively higher costs compared to traditional DMARDs. The ASPIRE study which compared methotrexate monotherapy with methotrexate, infliximab combination therapy showed a significant reduction in unemployment at 1 year in those on combination therapy compared to monotherapy (14% unemployed vs. 8% unemployed). The study also showed that those patients receiving combination therapy had a significantly higher likelihood of employability (Odds ratio 2.4). Significantly fewer employed patients receiving combination therapy reported lost working days than those on monotherapy and 79% vs. 67% of patient on monotherapy reported no lost working days during 1 year of treatment. [Smolen et al 2006]

1.1.7.1 Mortality

Several studies have shown that there is an increase in premature mortality associated with RA. [Arnett et al. 1988; Fries et al. 1980; Symmons et al. 1994; Wolfe et al. 1994] The standardised mortality rate (SMR) associated with RA is approximately 50% higher than the general population, with similar SMRs of about 1.2-1.3 in inception cohorts and 1.6-1.7 in non-inception cohorts seen over 60 years. [Sokka et al. 2008]

The attributable causes of death in RA patients does not seem to have changed greatly over the last few years and is in some ways similar to the general population with cardiovascular disease as the leading cause of death in RA patients, albeit at an earlier age compared to the general population. This has led to a renewed interest in the association of increased cardiovascular risk in RA patients over the last few years with a rise in the number of studies looking at the possible causes for this apparent association. [Cavagna et al. 2012; Kerola et al. 2012; Arts et al. 2012] Infections, respiratory and renal disease as attributable causes of death are more common in RA than the general population. In the UK 760 deaths were recorded as related to RA (Office of National Statistics 2005), this may be an underestimation of mortality rates as RA may not appear on the death certificate.

Patients with severe active RA are most likely to die early and those with clinical measures indicating more severe disease are prognostic for premature mortality. The most significant predictors of premature death appear to be worse functional and global assessments as well as co morbidities. [Sokka et al. 2008]

1.1.8. Treatment

The aims of treatment in RA should be to reduce pain, reduce disability and improve function, improve quality of life, retard disease progression and joint damage by disease modification and finally to improve prognosis. The management of RA should be provided by a multidisciplinary team and includes patient education, physical therapies such as occupational therapy, physiotherapy and podiatry, in conjunction with medication, surgery, psychological and social support. NICE guidance on the management of RA was published in 2009 [NICE clinical guideline

79] which emphasises a patient centred approach, regular specialist reviews, early combination treatment with DMARDs, access to surgery when needed and access to a multidisciplinary team.

1.1.9. Non-Pharmacological Interventions

1.1.9.1. Occupational Therapy

Occupational therapists (OTs) provide help for RA patients in a variety of ways. They predominantly help with common activities of daily living through the provision of aids but more specialist areas of occupational therapy such as hand therapy can improve hand function in RA patients. [Mathieux et al. 2009]

OTs who specialise in hand therapy have a particularly important role in the management of RA patients. They can assess patients in the early stages of RA and give advice about exercises and joint protection. They can also make and supply specialist splints to help support and rest the hand and wrist joints. Even later in disease hand therapists have a role in improving function of the hands and reducing pain through exercises, wax baths and splints. Tripoint rings can improve function in patients with swan neck deformities; they are splints which look like jewellery and keep the PIP joint lined up, protect the joint from hyperextending, and still allow the PIP joint to bend.

1.1.9.2. Physiotherapy

Before the days of effective DMARDs many RA patients were prescribed bed rest as treatment for their inflamed joints. Although rest and joint immobilisation can help an inflamed joint, prolonged rest can lead to muscle weakness. The aims of physiotherapy are to prevent disability, to increase functional capacity, to provide pain relief, and to provide patient education. Physiotherapy aims to maintain, improve and restore function through exercise. Physiotherapists use a combination of techniques when treating RA patients. These include physiotherapy techniques; hot and cold applications, hydrotherapy and electrical stimulation (eg Transcutaneous electrical nerve stimulation (TENS) therapy) as well as rehabilitation techniques; rest and splinting, assistive devices such as walking sticks, massage therapy, therapeutic exercise as well as patient education. [Reese 1958]

1.1.9.3. Podiatry

Podiatrists also have a role in early RA, as early podiatric intervention has been shown to improve foot pain and function. [Woodburn et al. 2002] The podiatrist has a number of roles in RA patient care at all stages of RA. In the early stages they can give advice about foot hygiene and footwear as well as providing customised orthoses and insoles to improve foot and toe posture and function. They can also help with toe nail trimming as well as minor surgery. In later stages of disease they can also provide specialist footwear.

1.1.9.4. Surgery

Despite the improvement in available treatments for RA, surgery still plays a major role for many patients. A variety of procedures are used by surgeons and many specialise in specific regions, notably hand surgeons. One of the most common procedures is joint replacement or arthroplasty; the joints which can be replaced include hip, knee, elbow, shoulder and MCP. Some joints which are not amenable to replacement such as the wrist and ankle can be fused which stabilises the joint as well as providing pain relief, although does lead to a reduction in joint movement. Surgery is required to stabilise atlanto axial subluxation which is one of the more serious complications of RA.

Surgical decompression can help entrapment neuropathies often associated with RA such as carpal tunnel syndrome. Specialist hand surgeons use a variety of techniques to improve severe deformities so as to improve hand function in RA patients, such as tendon tightening, loosening or repair as well as fusing hand or wrist joints or replacing MCPs.

1.1.10. Pharmacological Interventions

Several classes of drugs are used in the treatment of RA. These can be divided into the following groups: Analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease modifying anti-rheumatic drugs (DMARDs) and biologic therapies.

The old treatment pyramid approach for RA [Wilske et al. 1989] which consisted of initial ‘first line treatment’ with symptomatic drugs such as analgesics and NSAIDs, then only adding DMARDs later has now been completely turned on its head. This approach was based on the assumption that there was a gradual decline in quality of life and good health over time in RA; however, it has clearly been shown that there is a rapid decline in health and quality of life after the onset of RA. Therefore early and aggressive treatment with combination DMARDs is now recommended. [NICE clinical guideline 79]

1.1.10.1. Analgesics

Analgesics are painkillers that can be used to symptomatically help the pain associated with RA. They can be used in combination with other drugs such as DMARDs. There are several types of analgesics available including paracetamol, codeine, tramadol and opiate analgesics. Paracetamol and codeine are often used in combination with differing strengths of codeine such as co-dydramol and co-codamol.

1.1.10.2. Corticosteroids

Steroids have a powerful anti-inflammatory effect and are one of the quickest acting drugs used in RA. They are often used early in disease in combination with DMARDs which have a slower onset of action and are commonly used to rapidly suppress inflammation if disease flares. The main problem which limits their use is the well documented side effects associated with prolonged use. These include cataracts, adrenal suppression, hypertension, fluid retention, musculoskeletal (osteoporosis, myopathy and avascular necrosis) and metabolic (diabetes, hyperlipidaemia and obesity) effects.

1.1.10.3. Disease Modifying Anti-Rheumatic Drugs (DMARDs)

DMARDs are a group of unrelated drugs which are defined by their use in RA to slow disease progression. These drugs are distinct from anti-inflammatories which simply reduce inflammation without having an effect on the course of disease. Although these drugs were first used in RA their use has become much more widespread and they are used in other inflammatory conditions including other types

of inflammatory arthritis as well as connective disease diseases and inflammatory bowel disease. It is not clear how some of the drugs used in RA exert their effect and in fact only two DMARDs were developed specifically for RA; oral auranofin (no longer used) and leflunomide. A list of current DMARDs and their mechanisms of action are listed in Table 1.5.

Table 1:5 DMARDS and Their Mechanisms of Action

DMARD	Proposed Mechanism
Azathioprine	Purine synthesis inhibitor
Ciclosporin	Inhibits calcineurin and reduces T lymphocytes
D-Penicillamine	Unclear but felt it inhibits proliferation of T lymphocytes
Gold Salts	Felt to be similar to D-penicillamine
Hydroxychloroquine	Interference with antigen processing
Leflunomide	Pyrimidine synthesis inhibitor (dihydroorotate dehydrogenase inhibitor)
Methotrexate	Inhibits metabolism of folic acid (dihydrofolate reductase inhibitor)
Sulfasalazine	Possible Inhibitor of NF-kappaB

All DMARDs have side effects some of which are fairly minor such as nausea and diarrhoea but many can have potentially serious side effects requiring regular monitoring of patients receiving such drugs. These side effects include bone marrow suppression, hepatitis and rarely fulminant liver failure, hypertension, pneumonitis and an increased risk of infection.

Methotrexate is now probably the most widely used DMARD in RA. It can be used as monotherapy as well as in various combinations. When new studies are designed for new drug treatments in RA, methotrexate is used as standard therapy and in the trials of new biologic therapies, methotrexate is usually trialled in combination with any new drug.

DMARDs are now used early in disease and there is good evidence that combinations of DMARDs are better from the outset than monotherapy DMARDs. [Verhoeven et al. 1998] Common combinations include so called ‘triple therapy’; methotrexate, sulfasalazine and hydroxychloroquine [O’Dell et al. 1996] as well as

ciclosporin and methotrexate. [Choy et al. 2008] Those patients who fail to respond to good doses of combination therapies should be considered for biologic therapies.

1.1.10.4. Biologic Therapies

The introduction of biologic therapies has revolutionised the treatment of RA over the last two decades. These new therapies stemmed from a better understanding of the pathogenesis of RA and the important inflammatory pathways involved in the establishment and maintenance of disease. These therapies have been shown to improve signs and symptoms of RA as well as reduce progression of joint damage. The first biologic therapies to become available were anti-tumour necrosis factor alpha (TNF- α) drugs. These drugs are still widely used today and are usually considered the first line biologic therapy. Shortly after anti-TNF therapy became available, the drug Anakinra came onto the market, which targets interleukin-1 (IL-1). Although it was felt that both TNF- α and IL-1 were the most important cytokines in the inflammatory pathway in RA, Anakinra has not proven as efficacious as anti-TNF therapy.

Despite the undoubted success of anti-TNF therapy, it has failed to become the ‘cure’ that it was once heralded. There are also problems with anti-TNF therapy, the most common of which is the increased risk of infection and the particular problem of reactivation of tuberculosis (TB). Anti-TNF therapy can also worsen heart failure and a significant proportion of patients do not respond to therapy. Therefore, there has been ongoing research to identify other potential targets in the inflammatory pathway. A number of newer biologic therapies have come onto the market in the last few years. These include anti-B cell therapy, T cell co-stimulation blockade and anti-IL-6 therapy.

Conventional drugs inhibit small molecules; however, as cytokines are large peptides, large molecules are required to inhibit them. Therefore, biologics are large proteins based on immunoglobulins and are delivered by infusion or injection. The bioengineering required to produce these drugs is expensive and contributes to their significantly higher costs as compared to traditional DMARDs. Ideally these

biologics would be replaced with small molecules which can inhibit the intracellular targets of cytokines. However, this ideal is still some way into the future.

1.1.10.5. Tumour Necrosis Factor-Alpha (TNF- α)

Indications: TNF- α inhibitors should be considered when patients continue to have active disease despite an adequate trial of DMARDs. In the UK, the recommendations for the use of biologics by the national Institute for Health and Clinical Excellence (NICE), state that TNF- α inhibitors should be used when a patient has active disease as defined by a DAS28 score of 5.1 or above on at least two occasions one month apart; despite a trial of at least two DMARDs, one of which must be methotrexate. A 'trial' is considered to be six months unless the drug was stopped due to intolerance. [NICE guidance TA130] TNF- α inhibitors can be added to existing DMARD therapy, particularly methotrexate. In some cases TNF- α inhibitors can replace DMARDs, particularly if intolerance to DMARDs is a problem. At present in the UK, TNF- α inhibitors are not recommended as first line agents in the treatment of RA, however, there are many clinical trials ongoing which are looking at their use in early RA, which in part are looking at the possibility of turning off inflammation early in the disease process.

Infliximab: Infliximab is a chimeric IgG1 anti-TNF- α monoclonal antibody in which the antigen-binding region is derived from a mouse antibody and the constant region from a human antibody. It binds with high affinity to both soluble and membrane bound TNF- α . Infliximab exerts its effect in two different ways; firstly it interferes with binding of TNF- α to its receptor, secondly it can kill cells that express TNF- α via antibody dependent, complement driven pathways. Infliximab is given by intravenous infusion and the standard dose in RA is 3mg/kg every eight weeks after initial front loading. Although trough levels of infliximab are usually seen at eight weeks, the pharmacokinetics of infliximab can vary hugely between patients. Therefore, in patients whose symptoms return prior to their next infusion, reducing the time between doses may be effective at increasing trough levels and therefore improving efficacy. Certainly studies have shown a benefit in reducing the interval time in patients who lose efficacy with infliximab and some success has also been found with increasing the dosage of infliximab. [Flendrie et al. 2007]

Etanercept: Etanercept differs from infliximab in that it is a TNF-receptor fusion protein rather than a monoclonal antibody. It comprises two dimers; each dimer has an extracellular, ligand-binding portion of the higher-affinity type 2 TNF receptor (p75) which is linked to the Fc portion of human IgG1. Initially a monodimeric drug was engineered but this did not have sufficient biologic activity. Etanercept exerts its effects by binding to both TNF- α and TNF- β , preventing them from interacting with their receptors. Etanercept was initially given at a dose of 25mg twice a week subcutaneously, but over the last couple of years a once weekly dosing of 50mg has been introduced.

Adalimumab: Like infliximab, adalimumab is an IgG1 anti-TNF- α monoclonal antibody; however, it differs from infliximab in that it is fully humanised. Like infliximab it exerts its effects in two different ways; it binds with high affinity to TNF- α and consequently inhibits its binding to its receptors, it can also lyse cells which express TNF- α on their surface. Unlike infliximab, adalimumab is given subcutaneously once every two weeks. Peak absorption is reached by 120 hours, although this can vary widely between patients.

Other Anti-TNF Therapies: Since the introduction of anti-TNF therapies several new drugs have come to the market as possible treatment for RA. Specifically Certolizumab [Choy et al. 2002] and Golimumab [Keystone et al. 2009], both are anti-TNF- α monoclonal antibodies and they have recently been approved by NICE [NICE guidance 2010 and 2011].

Therapeutic Effects: TNF- α inhibitors can produce major improvements in symptoms and signs of RA. Improvements are typically seen within 12 weeks of commencement of treatment. There is no evidence that one TNF- α inhibitor is more effective than any other and other than patient choice with regards to administration, no particular reason for any specific agent to be used first.

In the UK, the NICE guidelines suggest TNF- α inhibitors should be continued provided the patient continues to show a treatment response which is defined as a

reduction in DAS28 of 1.2 or more from baseline. [NICE guidance TA 130] There are two types of non-responders; primary non-responders are those patients who fail to respond to a TNF- α inhibitor and secondary non-responders are those patients who initially show a response to treatment but then lose this effect. In patients who are primary non-responders, the drug should be stopped. It has been common practice to switch these patients who are primary non-responders to another TNF- α inhibitor. Evidence from biologic patient registers, such as the one in Sweden [STURE: van Vollenhoven et al. 2005] have shown that a substantial number of patients who switch from one TNF- α inhibitor to another for whatever reason will have a response to the second TNF- α inhibitor. In patients who are secondary non-responders, several different tactics have been employed, including increasing the dose of the TNF- α inhibitor, reducing the dosing interval or switching TNF- α inhibitor. Again, there is some evidence that increasing the dose or reducing the dosing interval is beneficial in these patients. However, guidance from NICE suggests that non-responders to a first TNF- α inhibitor should not be switched to another TNF- α but should be changed to anti-B cell therapy which is another type of biologic therapy and is discussed below. [NICE guidance TA 195]

There is growing evidence that TNF- α inhibitors slow radiographic progression of RA to a much greater degree than DMARDs alone. In some patients they seem to completely halt progression and the evidence for this is greater in patients with early RA and also in those patients who are also on concomitant methotrexate. The relationship between clinical and radiological response is not necessarily similar and as the effect of reducing radiological damage but not reducing clinical signs and symptoms is not clear in the long term, decisions should not be made solely on the benefits of radiological response.

Adverse effects: Some of the most common side effects seen with TNF- α inhibitors are local injection site reactions with etanercept and adalimumab. These usually present with redness and itchiness at the site of injection. Headaches and nausea are common with infliximab and are generally minor. Less commonly seen adverse effects are hypersensitivity like responses with infliximab such as urticaria, thankfully serious anaphylactic reactions are far more rare but well documented and

antihistamines, steroids and epinephrine should be available when infliximab is given.

An increase in infections are commonly seen in patients on TNF- α inhibitors, although there is debate on whether there is an increase risk of serious or opportunistic infections compared to those patients with severe RA treated with DMARDs or steroids. In those patients who develop a serious infection the TNF- α inhibitor should be stopped and a new TNF- α inhibitor should not be started if the patient has an infection. Some of the more common infections seen in patients taking TNF- α inhibitors are respiratory tract infections, skin infections including cellulitis and abscesses and septic arthritis, including infected prosthetic joints and osteomyelitis. These have been recorded and reported in the UK by the British society for rheumatology rheumatoid arthritis register. [Galloway et al. 2011; Galloway et al. 2013; Galloway et al 2011]

1.1.10.6. Other Biological Therapies

Other biological therapies now approved for use in RA after failure of anti-TNF therapy include Rituximab which is a monoclonal antibody directed against CD20 positive B cells [Leandro et al. 2002], Abatacept which is a co-stimulation blocker [Pollard 2007], preventing activation of T-cells and Tocilizumab [Maini et al. 2006] which is a monoclonal antibody directed against IL-6. All have shown efficacy in treating RA and are recommended by NICE. Rituximab is recommended as the next drug to be used if a patient has failed anti-TNF therapy and abatacept and tocilizumab are recommended for patients who have failed Rituximab [NICE Guidance 2010].

1.2. DISEASE ASSESSMENTS IN RHEUMATOID ARTHRITIS

1.2.1. Joint Swelling and Tenderness

Swollen joints in RA are a result of inflammation and therefore reflect disease activity. Swelling in RA joints is due to a combination of synovial thickening/inflammation (synovitis) and joint effusion. Swelling in RA joints is often described as fluctuant and should not be mistaken for hard bony swellings such as those seen in nodal osteoarthritis or the apparent swelling of joints due to

subluxation, such as that seen in the metacarpophalangeal joints of RA patients with subsequent uncovering of the head of the metacarpal giving the appearance of swelling. Several studies have shown there is often inter-observer error when measuring swollen joint counts, so in trials ideally the same person should assess swollen joint counts on each visit.

A tender joint in RA is defined as a joint where pain is felt either at rest when pressure is applied by an assessor, or by movement of a joint or by questioning about joint pain. The amount of pressure applied by the assessors thumb and index finger to the joint should be sufficient to turn the assessor's nail bed 'white'. There is less inter-observer error in assessing tender joints in RA patients. Classically an active inflamed joint in RA is both swollen and tender, however, in routine practice some patients will have some swollen joints which are not tender and conversely and perhaps more commonly some patients will have significantly more tender joints than apparent swollen joints. The cause of the discrepancy between swollen and tender joints is not clear; some have suggested that in those patients with large number of tender joints this may be due to the coexistence of fibromyalgia, so called 'fibromyalgic RA' [Wolfe et al. 2004].

Several indices measure swollen and tender joint counts. These differ in the joints assessed and some also grade the amount of tenderness in a joint. The most commonly used are the American College of Rheumatology (ACR) extended 66/68 counts for swollen/tender joints, the Ritchie Articular index [Ritchie et al. 1968] and the reduced 28 joint count [Fuchs et al. 1989]. As there seems to be no advantage in measuring large numbers of joints the reduced 28 joint count is becoming the most widely used method of joint count (Figure 1.1).

ACR 66/68 Joint Count

Upper Limb:

Temporomandibular (n=2), sternoclavicular (n=2), acromioclavicular (n=2), shoulder (n=2), elbow (n=2), wrist (n=2), metacarpophalangeal (n=10), interphalangeal of the thumbs (n=2), proximal interphalangeal (n=8) and distal interphalangeal joints (n=8).

Lower Limb:

Hip (n=2), knee (n=2), ankle mortise (n=2), ankle tarsus (n=2), metatarsophalangeal (n=10), interphalangeal of great toe (n=2), proximal/distal interphalangeal joints (n=8).

Joint tenderness is assessed as being present or not. The 66 joints to be examined for swelling are the same as those examined for tenderness, except the hips joints are excluded.

The Ritchie Articular Index (RAI)

Upper Limb

Temporomandibular (treated as a single unit), cervical spine, sternoclavicular (treated as a single unit), acromioclavicular (treated as a single unit), shoulder (n=2), elbow (n=2), wrist (n=2) metacarpophalangeal (each side treated as a single unit) and proximal interphalangeal joints (each side treated as a single unit).

Lower Limb:

Hip (n=2), knee (n=2), talocalcaneal (n=2), midtarsal (n=2), metatarsophalangeal joints (each side treated as a single unit).

Tenderness is graded 0-3 (0 - no tenderness, 1 - patient complained of pain, 2 - patient complained of pain and winced, 3 – patient complained of pain, winced and withdrew)

The 28 Joint Count

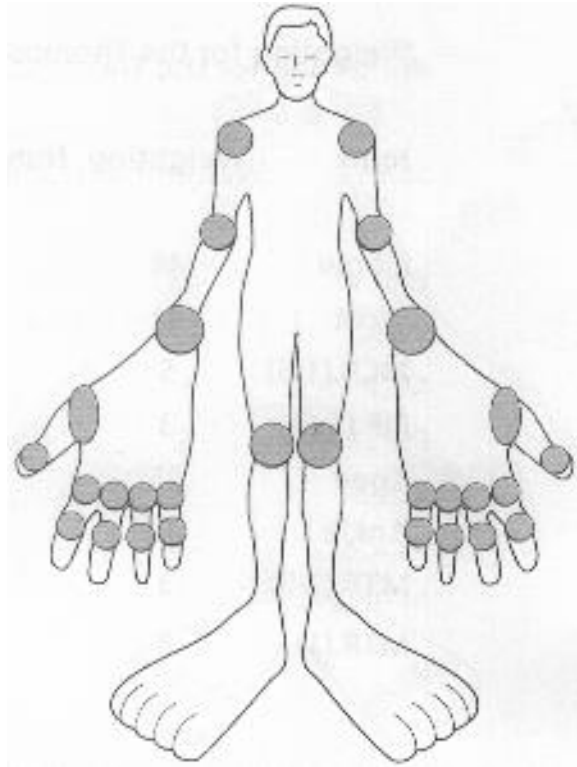
Upper Limb:

Shoulder (n=2), elbow (n=2), wrist (n=2), metacarpophalangeal (n=10), interphalangeal joints of thumb (n=2) and proximal interphalangeal joints (n=8)

Lower limb:

Knee (n=2), Tenderness is assessed as being present or not. The same 28 joints are assessed for swelling.

Figure 1:1 Joints Used For 28 Joint Counts



The simplicity of the 28 joint count with its lack of grading makes it an appealing measure to use in routine clinical practice. Indeed Prevoo et al in 1993 compared a number of different joint counts and indices and found little difference in their validity and reliability, though indices which included weighting did not perform as well. In 1995 Smolen et al compared the 28 joint count with the extended ACR 66/68 joint count in a prospective study of 735 RA patients. They concluded that the joints chosen in the 28 joint count were those most commonly involved in RA and the two indices were highly correlated. These studies show that the 28 joint count is the preferred method as it is not only as valid and reliable as the 66/68 joint count but is also easier and quicker to perform. A potential problem however, with the 28 joint count is that the feet are not included and for some patients the feet may be their predominant problem area and this will need to be taken into account.

1.2.2. Patient and Physician Global Assessment

Global assessments, usually in the form of double anchored visual analogue scales (Figure 1.2) are widely used in routine clinical practice and clinical trials. There has recently been a call to standardise the question asked when assessing patient global assessment to ensure a more accurate score. The advantage of a patient global assessment is that it is quick and simple to use and score, the disadvantages are that scores are often highly correlated with pain visual analogue scores and may not be a true reflection of disease activity as the score may also be influenced by RA factors; this may be improved by careful explanation to the patient. The physician global assessment of disease activity is often not used formally in routine clinical practice, but clearly this is automatically taken into account by the physician when making treatment decisions as the physician is able to consider the impact of other co morbidities.

Figure 1:2 Visual Analogue Assessments



1.2.3. Laboratory Measures

Blood tests are frequently used in the management of RA. Patients often undergo regular blood tests as part of DMARD monitoring but they can also be used to monitor disease activity as well as help with diagnosis and prognosis. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly used to monitor disease activity as valid indicators of inflammation. Their main drawback is that they are not specific for RA inflammation and therefore can be influenced by concomitant infection or inflammation from a different source. Currently there is no specific test to monitor disease activity in RA. Other blood tests that reflect disease activity in RA include a rise in other acute phase proteins such as alkaline phosphatase (this is an important fact to remember as some non specialists may

mistake a rise in alkaline phosphatase as a side effect of drug treatment), ferritin, platelets and immunoglobulins. Conversely active disease in RA can be associated with a reduction in haemoglobin and albumin.

A persistently raised acute phase protein in RA is an important observation to make as there is good evidence that these patients have a worse prognosis. There is good correlation between raised ESR and CRP with clinical measures, although this is predominantly with swollen joint counts rather than tender joint counts [Thompson et al. 1987; van Leeuwen et al. 1994]. Continued elevation of ESR and CRP are also associated with more rapid radiological progression compared to those RA patients with a normal ESR and CRP. This increased radiological progression has been shown in both early disease [van Leeuwen et al. 1994] as well as more longstanding disease [Hassell et al. 1993].

Although in general acute phase proteins provide a good marker of disease activity in RA, some patients may only have small joint involvement which may not mount a large enough inflammatory response to be detected and in a small number of patients despite evidence of widespread synovitis clinically, there is no significant rise in acute phase proteins.

Blood tests useful in the diagnosis and prognosis of RA include rheumatoid factor and the more recently described anti-cyclic citrullinated peptide (anti-CCP) antibodies. Rheumatoid factor is an immunoglobulin directed against the Fc portion of IgG. It is reported as being positive in about 70-80% of RA patients although negative results do not rule out disease. [Wolfe et al. 1991] Rheumatoid factor may be seen in other rheumatological diseases particularly Sjogren's syndrome but also SLE and non rheumatological conditions such as hepatitis C. Low titres of rheumatoid factor can also be seen in the normal population with increasing incidence with age in the absence of any pathology.

The need to identify RA patients early led to the development of anti-CCP antibody test. Blood tests and x-rays may be normal in up to 60-70% of patients with early RA [Emery 1994] and rheumatoid factor has only low sensitivity and moderate

specificity in diagnosing RA [van Zeben et al. 1992]. In the last 10 years it has been discovered that RA patients develop antibodies to modified (citrullinated) arginine residues, and this has resulted in the development of the anti-CCP antibody test, which has a sensitivity of 68% and a specificity >97% [Schellekens et al. 2000]. Further improvement in the testing method has improved the sensitivity to about 80% and the specificity >98% [van Venrooij et al. 2002]. It has also been shown that 35-40% of rheumatoid factor negative patients are anti-CCP antibody positive. Anti-CCP antibodies also have prognostic implications as studies have shown that they along with rheumatoid factor, ESR and female gender are independent predictors of radiographic progression. Patients with high levels of anti-CCP antibodies seem particularly prone to radiographic progression [Syversen et al. 2008].

1.2.4. Using Multiple Measures to Assess Disease Activity

1.2.4.1. Core Data Set

In RA no single measure is universally appropriate. As there remains no cure for RA, treatment aims to reduce symptoms and slow disease progression. Previously clinical trials in RA would include different outcome measures to assess response to treatment. This made comparing trials and results impossible, therefore there was a drive to have a consensus view on a 'core data set' of outcome measures which should be included in every clinical trial in RA. Both the OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) initiative [Tugwell et al. 1993] and EULAR (European league against rheumatism) [Smolen 1992] set up working groups to decide on the preferred outcome measures that should be included in the core data set. The outcome measures included in the core data set include measures of disease activity (swollen and tender joint counts, patient and physician global assessment, pain assessment and acute phase markers), functional assessment (HAQ) and radiological assessment of disease progression. (Table 1.6) At the last OMERACT meeting there was a call to include more patient centred outcomes in the core data set, following this meeting it was agreed that fatigue should be added to the core data set for every clinical trial in RA [Kirwan et al. 2007].

Table 1:6 OMERACT and EULAR Core Data Set for RA

Number of swollen joints
Number of tender joints
Pain assessed by the patient
Patient's global assessment of disease activity
Assessor's global assessment of disease activity
Laboratory evaluation (ESR, CRP, or equivalent)
Self administered functional assessment (<i>eg</i> HAQ)
X-ray assessment for joint damage

1.2.4.2. Composite Measures of Disease Activity

Composite indices incorporate several outcome variables into one simple measurement which has major advantages in both clinical trials and routine practice. Several composite measures have been designed over the years dating back to 1958 (Table 1.7). Two composite measures have been widely incorporated into clinical trials (Table 1.8). One is the ACR response criteria which were developed by Felson et al to simplify the assessment of response in clinical trials. [Felson et al. 1995] They use components of the core data set and involve improvements in both swollen and tender joint counts and three out of: patient global assessment, physician global assessment, pain, ESR and a functional measure such as HAQ. Improvements can be at 20%, 50% or 70% levels (termed ACR-20, ACR-50 and ACR-70 responses). The main drawback with the ACR response is that it is categorical and not a continuous measure and its primary use is in clinical trials of drug treatments in RA.

The other is the Disease Activity Score (DAS) [van de Heijde et al. 1993]. The initial DAS score included a 44 swollen and tender joint count but this has now been modified for use with 28-joint counts for tenderness and swelling [Prevoo et al. 1995], making it simpler to use and it is equally as valid as more comprehensive articular indices, which can be time consuming in routine practice.

The DAS28 formula is:

$$0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \ln(ESR) + 0.014 \times (PGA).$$

Table 1:7 Composite Disease Activity Scores

Year	Authors	Main features
1958	Lansbury	EMS, fatigue, aspirin consumption, grip strength, ESR, Haemoglobin
1956	Lansbury and Haut	As above plus area weighted articular index
1981	Mallya and Mace	An index of disease activity
1990	Davis	Stoke index
1990	Van der Heijde	DAS
1990	Stewart	The index of disease activity
1993	Jones	Modified Stoke index
1995	Symmons	Overall status in RA (OSRA) - activity and damage score
1995	Prevoo	Modified DAS (for 28-joint counts)

The DAS28 gives a continuous measure with lower numbers indicating less disease activity. The DAS28 can also be categorised into mild (score ≤ 3.2), moderate (score > 3.2 and ≤ 5.1) and severe disease (score > 5.1). Response to treatment can also be categorised into no response (improvement ≤ 0.6 and DAS > 3.7), moderate response (improvement ≤ 1.2 and > 0.6 , and DAS > 2.4 and ≤ 3.7) and good response (improvement > 1.2 and DAS ≤ 2.4). The DAS28 has become the most important composite measure in the UK as eligibility for biologic therapies depends on severe active disease as defined by a DAS28 of > 5.1 on two occasions, therefore the DAS28 is now often measured routinely in clinical practice. Although there have been criticisms of the DAS28, particularly for its calculation which puts greater emphasis on tender joint counts rather than swollen joint counts, it remains the most widely used composite measure in routine clinical practice and currently there appears to be no better alternative.

Table 1:8 ACR Response Criteria and the DAS28

ACR Response Criteria ≥20%/50%/70% Improvement in:	Swollen Joint Count Tender Joint Count Improvement in at least 3 of the following <ul style="list-style-type: none"> • Patient global assessment • Physician global assessment • Patient pain scale • Health assessment questionnaire • ESR or CRP
DAS28	Swollen joint count (28 joints) Tender joint count (28 joints) ESR or CRP Patient global assessment
<i>Calculated using formula:</i> $0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \ln(ESR) + 0.014 \times (\text{patient global assessment})$	

1.2.4.3. Radiological Assessments

X-rays are used in routine clinical practice to help with diagnosis but also to assess disease progression. Several scoring methods to assess the amount of joint damage in RA have been employed over the years. Despite simplifying the number of joints used to focus on joints most commonly affected in RA the scoring methods remain time intensive and are not suitable for routine use [Kaye 1991] but are commonly used in clinical trials to determine the reduction in disease progression over time. The two x-ray scoring methods widely used are the Sharp scoring method [Sharp et al. 1971] and the Larsen scoring method. [Larsen et al. 1979]

The Sharp Score

In 1971 Sharp [Sharp et al. 1971] first described a scoring method which included the hands and wrists. In total 29 areas were assessed for erosions and twenty seven areas for joint space narrowing. Erosions were graded 0-5 and joint space narrowing graded 0-4. This original scoring method has since been modified several times and the original scoring method is no longer used. The modification proposed by Sharp et al in 1985 is currently considered the standard for the Sharp method. The modified version has been simplified and includes 17 areas for assessment of erosions and 18 areas for assessment of joint space narrowing again the hands and wrists. Each

erosion scores one point up to a maximum of 5 for each area. Joint space narrowing is still graded 0-4 with ankylosis of a joint scoring 4 points. Subluxation is not scored. In 1986 Fries et al, suggested a further modification, which gives more weight to erosions compared to joint space narrowing. Erosions scores are combined with the worst joint space narrowing scores from 6 areas. In 1987 Kaye et al, proposed a further modification to the Sharp score which included scores for dislocation or marked subluxation. Van der Heijde further modified the Sharp score in 1999 [van der Heijde 1999] by including feet in the assessment although hands had greater weighting because more joints are scored and subluxation was again included.

The Larsen Score

In 1974 Larsen [Larsen 1974; Larsen 1975] first developed a method of scoring based on comparison of patients x-rays with a standardised set of reference films. The method gives an overall measure of joint damage as the joints are categorised into six stages from 0 (normal) to 5, which reflect the gradual progression of joint damage. The original method has undergone several modifications between 1977 and 1995. The six different stages described in the 1977 version [Larsen et al. 1977] are as follows: Grade 0 = normal; grade 1 = slight abnormalities (periarticular soft tissue swelling and periarticular osteoporosis and slight joint space narrowing); grade 2 = definite early abnormalities; grade 3 = medium destructive abnormalities; grade 4 = severe definite abnormalities; and grade 5 = mutilating abnormalities. Larsen further modified the scoring system so as to be useful in evaluating x-rays in long term studies. The main differences suggested in the 1995 modification were to delete the scores for the thumbs and great toes, divide the wrists into four quadrants and a grading system for the size of erosions. The grading scale ranges from 0-5 with an overall score range of 0-160 and is summarised in the Table 1.9.

Table 1:9 Larsen Grading System for Erosions

Grade	Assessment
0	Intact bony outlines and normal joint space
1	Erosion less than 1mm in diameter or joint space narrowing
2	One or several small erosions (diameter more than 1mm)
3	Marked erosions
4	Severe erosions (usually no joint space left and the original bony outlines are only partly preserved)
5	Mutilating changes (the original bony outlines have been destroyed)

Scott et al proposed a modification to the grading system of the Larsen score in 1995. The changes were to the grades 1-4 with grade 0 and 5 left unchanged; this was felt to allow a higher correlation of grade 1 between raters.

Although plain radiographs are still the most common method by which RA progression is monitored there are disadvantages including variability of radiographic techniques, the difficulty in scoring radiographs despite the systems described above and the relative insensitivity of plain radiographs to detect changes in early RA. More recently ultrasound (US) and magnetic resonance imaging (MRI) have been shown to detect joint damage in RA earlier than plain radiographs and also give information regarding synovial thickening and active synovitis. The cost of MRI makes regular serial scans an unviable option in many cases; ultrasound (US) however is much cheaper and has been shown to correlate well with MRI in RA. The disadvantage of US is that it is operator dependent.

1.3. QUALITY OF LIFE IN RHEUMATOID ARTHRITIS

It is important to consider quality of life in RA as it is a chronic disease with no cure. RA can impact on many different aspects of life. It has physical impacts such as pain, fatigue and ultimately disability but it can also have an impact psychologically causing distress, depression and anxiety.

1.3.1. Pain

Pain remains the major concern for most patients with RA. Its persistence is an important negative consequence of disease. Although controlling pain is one indication of successful treatment, the majority of RA patients have significant amounts of pain despite therapy. Patients consistently rate pain as their most important symptom. [Heiberg et al. 2002] Other than drug studies looking at the effect of reducing inflammation, there are few studies which have specifically looked at pain pathways and the cause of chronic pain in RA patients. [Lee 2013]

Despite pain being a dominant symptom in RA it is not routinely measured and is not part of commonly used composite measures that assess RA such as the DAS28. The most common way of measuring pain is the double anchored 100mm visual analogue scale (VAS), labelled 'No pain at all' at one end, and 'Pain as bad as it could be' at the other end. The VAS was first developed in rheumatology in 1974 by Huskisson et al and takes only a few seconds to complete. The pain VAS is part of the American College Rheumatology (ACR) and EULAR/OMERACT core data set [Felson et al. 1993; van Gestel et al. 1996].

The verbal rating scale (VRS) is another simple measure which has been shown to correlate strongly with the VAS [Tugwell et al. 1992] The VRS consists of words which describe the severity of pain – such as 'none', 'mild', 'moderate', 'severe' and 'extreme'. This is not as widely used as the VAS although one study has shown that certain patients may prefer this to the VAS [Clark et al. 2003].

There are other more detailed pain questionnaires available which have been used in clinical studies and add much to the understanding of pain in RA. Their place in routine clinical practice is limited by the amount of time needed to complete the questionnaires. The McGill pain questionnaire [Melzack 1983] has 102 words in 20 categories and patients are asked to circle words that describe their current pain. The complete McGill pain questionnaire also has a diagram so that patients can indicate the location of their pain. There are also questions relating to the intensity of pain and how it changes with time. Although this questionnaire provides detailed

knowledge and insight into the pain experienced in RA it takes at least 15-20 minutes to complete. Even the short version of the questionnaire [Melzack 1987] is too long to use in routine clinical practice but is useful in the research setting. The rheumatoid arthritis pain scale (RAPS) was designed specifically to measure pain in RA [Anderson et al. 2001]. This 24 item questionnaire has 4 domains and is measured using a seven-point Likert scale. Like the McGill questionnaire, RAPS provides more information than the VAS but its use is limited to specialised clinical studies.

1.3.2. Fatigue

Fatigue is common in rheumatoid arthritis (RA) and its absence characterises disease remission [Pinals et al. 1981]. Qualitative studies have highlighted the importance people with RA attribute to fatigue and RA patients believe reducing fatigue should be a key treatment aim [Carr et al. 2003; Ahlman et al. 2005] and patients regard fatigue as a major determinant of their quality of life [Rupp et al. 2004] and disability [Scott et al. 2005]. Between 40-80% of RA patients attending specialist clinics have clinically relevant fatigue, which is a feature of active disease. [Belza 1995; Belza et al. 1993; Pinals et al. 1981; Wolfe et al. 1996] By contrast few cases (under 5%) are in remission [Balsa et al. 2004], in which there is no fatigue. These observations suggest disease activity is one underlying factor, in the pathogenesis of fatigue in RA. Surprisingly the ways in which disease activity influence RA fatigue has not been investigated to any extent. However, interest in this issue has been stimulated by a large randomised controlled trial (RCT) of adalimumab, an anti-TNF agent, which significantly reduced fatigue in RA [Weinblatt et al. 2003]. The improvement in fatigue was associated with falls in disease activity, providing the best evidence yet that inflammatory synovitis is a potentially important causal factor for RA fatigue. There is relatively little data on whether conventional disease modifying anti-rheumatic drugs (DMARDs) reduce fatigue. Only one RCT has looked at this to any extent. It compared leflunomide with methotrexate and showed both DMARDs improved SF-36 energy and vitality scores, which are equivalent to fatigue measured with specific instruments [Strand et al. 2005].

Several other factors influence RA fatigue, including psychosocial factors, health beliefs, illness perceptions and poor social support [Huyser et al. 1998; Riemsma et

al. 1998]. Fatigue also has strong relationships to pain and depression [Belza 1995; Belza et al. 1993; Wolfe et al. 1996; Huyser et al. 1998; Riemsma et al. 1998; Rupp et al. 2004; Tack 1990; Fifield et al. 1998; Wolfe et al. 2004; Suurmeijer et al. 2001; Fifield et al. 2001; Crosby 1991; Jump et al. 2004]. These inter-relationships led Wolfe to coin the term "fibromyalgic RA" to describe the sub-set of patients with high levels of fatigue, pain and depression [Wolfe et al. 2004]. Previous studies have also shown that high fatigue scores are associated with greater levels of disability [van Hoogmoed et al. 2010]. This finding might be explained by fatigue being a marker of disease activity. Alternative explanations for the relationship of fatigue to disability include the interaction of fatigue with psychological symptoms or perhaps a more direct link to disability.

Despite these findings fatigue is not routinely measured in clinical practice or in studies. Also, there is no agreement on the most appropriate measure of fatigue in RA, but the most commonly used instrument is the VAS. Like the pain VAS it usually takes the form of a double anchored 100mm scale, labelled with 'No tiredness' at one end and 'Absolutely no energy at all' at the other end. This is a simple and easily reproducible method of measuring fatigue but does not capture the multidimensionality of fatigue in RA.

1.3.2.1. Measuring Fatigue in Rheumatoid Arthritis

There are a number of multidimensional instruments available that measure fatigue but no consensus on the most appropriate instrument to use in RA. Most multidimensional instruments were designed for use in other chronic illnesses but have been applied to RA. Two of these measures have been validated in RA. The first of which is the multidimensional assessment of fatigue (MAF) [Belza et al. 1993]. This is a 16 item scale with 4 domains; severity, distress, degree of interference of daily living and timing.

The other validated instrument is the functional assessment of chronic illness therapy –fatigue scale (FACIT-F) [Cella et al. 2005], which has 13 questions with 4 domains; general, physical, mental fatigue and vigour. Other multidimensional instruments that have been used include an instrument developed for cancer (the MFSI) [Stein et

al. 1998], the Chalder fatigue scale [Chalder et al. 1993], and the fatigue symptom inventory [Hann et al. 1998]. Generic health measures such as the SF-36 which can be used in any disease also have subscales (energy and vitality) that measure fatigue, though these are less specific. There are no reported head to head comparisons of all these instruments. However, Wolfe [2004] has shown that in RA the VAS performs well in comparison to the MAF, energy and vitality scale of the SF-36 and brief fatigue inventory, in terms of sensitivity to change and correlation with clinical variables.

These patients had substantially worse quality of life. Clearly further work focusing specifically on fatigue in RA is needed, specifically, to determine the most appropriate instrument.

1.3.3. Fibromyalgic Rheumatoid Arthritis

Rheumatoid arthritis (RA) spans several distinct clinical phenotypes. One of these includes coexisting fibromyalgic features; this phenotype has been termed “fibromyalgic RA” [Scott et al. 2007]. Very little research has been done in this area but Wolfe and colleagues [Wolfe et al. 1984; Wolfe et al. 2004] have highlighted its importance and concluded that in their cohort of 11,866 RA patients approximately 17% had fibromyalgic features. Fibromyalgia was detected using a regional pain scale and a fatigue VAS. These patients had more comorbidities, greater sociodemographic disadvantage, more severe symptoms, higher HAQ levels and worse quality of life than RA patients without fibromyalgic features. Clearly further work needs to be to determine whether this RA subtype does indeed exist; using objective measures such as tender points rather than just subjective scores.

The high pain and disability scores that are seen in fibromyalgic RA suggest that these patients will also have high scores using summative assessments such as the Disease Activity Score for twenty-eight joints (DAS28) which includes assessments of tender joint counts, swollen joint counts, ESR and patient’s global assessments. This perception is supported by previous research that shows DAS scores are often high in patients with fibromyalgia without RA [Leeb et al. 2004]. In this context DAS28 scores of 5.1 or more are considered indicative of active disease. DAS scores

are particularly important in treatment decisions about disease modifying anti-rheumatic drugs (DMARDs) and biologics [Meyer et al. 2007; Fautrel et al. 2008]. If DAS scores are disproportionately high in relation to the level of inflammatory synovitis in fibromyalgic RA, the value of DAS assessments in these patients is open to question. This is a particularly cogent issue as a recent study of fibromyalgic RA by Coury et al suggested DAS28 over-estimated disease activity in these patients [Coury et al. 2009].

1.3.4. Psychological Impacts

Depression, which is often associated with high levels of fatigue, has been identified as a problem for a large proportion of patients with RA [Zautra et al. 1994] and some studies have suggested that depressive symptoms are present in 25% or more of patients [Frank et al. 1988]. Many patients also have high levels of anxiety [VanDyke et al. 2004]. Depression has been shown to be associated with reduced health status, as well as higher pain and fatigue levels and reduced quality of life [Katz et al. 1993]. RA often causes chronic pain and the effects of chronic pain on patients' physical, psychological and social functioning are widely recognised [Anderson et al. 1985]. Factors other than pain have also been found to be important in psychological adjustment in patients with RA. Specifically social support is particularly significant in adjustment to RA given the limitations that physical disability may create. Social support has been found to minimise the effects of physical limitations resulting from RA [Doeglas et al. 1994; Goodenow et al. 1990]. The situation is further complicated by RA patients with a pre-existing history of an affective disorder such as depression; who have higher levels of fatigue and ill health, with self-efficacy playing an important mediating role in this relationship [Jump et al. 2004]. In early RA, if there are baseline symptoms of depression or anxiety, fewer patients achieve clinical remission compared with patients without these conditions. However, in early RA, patients who achieve DAS28 clinical remission experience an improvement in depression and anxiety symptoms [Kekow et al. 2011].

There are many different instruments that have been designed to assess depressive symptoms, such as the Hospital Anxiety and Depression score [Zigmond et al. 1983]

and the Beck Depression Inventory [Beck et al. 1961]. Despite the fact that these symptoms are common in patients with RA, they are very rarely documented or assessed in clinical practice and are only assessed in specialised studies.

Pain and disability inevitably affect patients' psychological status and general feeling of well-being. Although there is no evidence that patients have primary psychological disturbances, chronic illness may cause substantial long-term psychological effects. In a large study by Polsky et al in 2005 they examined the risk of developing significant depressive symptoms following a new diagnosis of a chronic illness over a six year period. In all illnesses there was a high risk of depressive symptoms developing in the first two years after diagnosis, although the risk decreased after this period. However, in patients with arthritis there was a significantly higher risk of developing depressive symptoms 2-4 years after diagnosis.

Comparative studies of different chronic diseases show that psychological functioning contributed to overall quality of life for all disorders, whereas physical and social functioning contributed in only some diseases [Arnold et al. 2004]. The relationship between disability and psychological morbidity is thus relatively specific for RA. Interestingly illness perceptions, which are an individualistic view of disease, may be key factors in determining the impact of RA [Groarke et al. 2004], according to the results of a small study of 75 women with RA. Depression was found to be associated with high use of coping by denial and with less frequent use of active coping, planning and seeking instrumental social support. It appears that illness perceptions have significant implications for adaptation to illness and outweigh the impact of medical disease status on depression, physical function and pain.

A recent EULAR initiated study has finalised and validated a patient derived composite measure of impact of RA [Gossec et al. 2011]. The rheumatoid arthritis impact of disease (RAID) score, takes into account pain, functional capacity, fatigue, physical and emotional wellbeing, quality of sleep and coping. Further studies are planned to examine sensitivity of change.

1.3.5. Disability

The increasing focus on patients' perspectives of their health [Heiberg et al. 2005; Kirwan et al. 2003] has resulted in an increasing interest in using health status measures to capture patients' views on their disease [Scott et al. 2000]. Disability in RA is usually measured with self-assessment questionnaires. Most clinicians use disease-specific measures, such as the Health Assessment Questionnaire (HAQ) [Wolfe 2000] or the Arthritis Impact Measurement Score (AIMS) [Meenan et al. 1980]. Alternatively, there are generic measures such as the SF-36 [West et al. 2005], the Nottingham Health Profile (NHP) [Uutela et al. 2003] and the EQ-5D [Picavet et al. 2004]. Although disease-specific measures are often preferred, generic measures can be used to compare across different diseases [Stavem et al. 2000], and have been shown to detect changes in early disease [Soderlin et al. 2004]. There is still no consensus on the best overall measure of quality of life in RA and new measures continue to be devised [Currey et al. 2003]. However, it would seem sensible to use a disease specific-measure in RA as generic measures can be insensitive with significant floor and ceiling effects. Although the AIMS questionnaire is disease specific it is somewhat complex to use and therefore has not been widely adopted. The HAQ has become the most widely used instrument and is relatively easy to use taking only a few minutes to complete and to score.

1.3.5.1. Health Assessment Questionnaire

The HAQ assesses disability in eight domains; dressing, arising, eating, walking, hygiene, reach, grip and common activities. There are twenty questions over the eight domains with four possible answers; without any difficulty, with some difficulty, with much difficulty, unable to do. Each of the disability items has a companion aids or devices variable, which is used to document whether the patient requires the assistance of a device and or the assistance of another person to perform each task. The HAQ can be seen in the appendix.

There are a number of variations to the original HAQ score, including the shortened modified HAQ [Pincus et al. 1983] and the shortened RA-HAQ, a study by Wolfe [Wolfe et al. 2001] of 2,491 clinic patients with RA with active disease showed the

conventional HAQ is better at detecting treatment change, and identifies the extent of functional disability better than the shortened questionnaires. The benefits of the MHAQ and RA-HAQ are that they are short and easier to score but this comes at a price, which is loss of sensitivity and loss of sensitivity to change.

An alternative termed the HAQ-II, which involves 10 items, has also been developed. This has been studied in 14,038 RA patients with rheumatic disease over a 2-year period [Wolfe et al. 2004]. It is reliable, has a longer scale than the conventional HAQ, and may therefore be better equipped to avoid floor and ceiling effects. Conversion from HAQ to HAQ-II and from HAQ-II to HAQ for research purposes is simple and reliable. [Anderson et al. 2010] The HAQ-II can be used in all places where the HAQ is now used, and it may prove to be easier to use in the clinic. Another modification of the HAQ is the multidimensional HAQ (MDHAQ), developed and validated on 688 patients by Pincus et al in 1999. One of the problems of the MHAQ and HAQ as mentioned above is the floor effect. The MDHAQ by adding 6 advanced questions on activities of living (ADL) to the 8 ADL included on the MHAQ aimed to overcome this floor effect. Whereas patients may report no problems performing simple tasks, they may experience difficulty performing advanced tasks. Also psychological items which assess depression, anxiety and poor sleep which are included may be used to screen for these common problems. The MDHAQ has been subsequently revised [Sokka et al. 2005] and the number of ADL items reduced to 10 items. This was found to provide similar information to the 14 item MDHAQ but to be more easily completed. The MDHAQ is a simple 2-page questionnaire that could be completed at every clinic visit and takes only seconds to score. It may be that the HAQ-II and MDHAQ will become more widely used over the next few years.

Another simplification in HAQ scores that has been suggested is using visual analogue scales to assess function. Wolfe and Michaud [Wolfe et al. 2005] studied 394 RA patients comparing HAQ, the HAQ-II, and a visual analogue functional scale. They found that the distribution differences between HAQ and HAQ-II and the VAS-F suggest that patients do not see minor limitations as problematic, but rate major limitations as being particularly limiting and worthy of high ratings. They

concluded that a visual analogue functional scale, which represents a patient-weighted functional assessment in which additional interpretation is given to the meaning of the limitations by the patient, may be suitable for use in the clinic and in research.

1.3.5.2. Arthritis Impact Measurement Scales

The Arthritis Impact Measurement Scales (AIMS) were developed by Meenan et al in 1980; they are a combination of pre-existing instruments such as the Rand Health Insurance Study Scales and the Quality of Well Being (QWB) scale and newly created health status scales which assess physical, emotional, and social well-being in nine dimensions: mobility, physical activity, activities of daily living, dexterity, household activities, pain, social activity, depression and anxiety. [Meenan et al. 1980] These nine dimensions can be combined to form three major health status components: physical function, psychological status and pain. A further 21 questions define general health, the patients' health perceptions, overall impact of arthritis, medication intake, co-morbidity and demographic data. The questionnaire takes approximately 15-20 minutes to complete and shorter versions exist and the original questionnaire has been 'anglicised' for use in the UK and has been extensively validated and translated into several different languages.

1.3.6. Generic Measures of Quality of Life

There are a number of different generic measures which have been designed to measure quality of life. The questionnaires capture different aspects of quality of life and as they are generic can be used in different diseases.

1.3.6.1. SF-36

The SF-36 [Ware et al. 1992; McHorney et al. 1993] is the most widely used generic measure of health status. [Garratt et al. 2002] The SF-36 can be self-administered or with the use of an interviewer. It can be completed in 5-10 minutes and has been applied to large populations in a number of countries and to patients with a variety of illnesses of all age groups. There are 36 questions in the SF-36, these items are grouped into 8 scales; physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional

(RE) and mental health (MH). There are 2 summary measures which aggregate the 8 scales; Physical Health (PF, RP, BP, GH) and Mental Health (VT, SF, RE, MH). All but one of the 36 items are used to score the 8 SF-36 scales. Each item is used in scoring only one scale. These 8 scales were selected from the 40 used in the Medical Outcomes Study, those chosen were felt to represent the most frequently measured concepts in widely-used health surveys and those most affected by disease and treatment. A shortened version of 12 items (SF-12) [Hurst et al, 1998] has been developed but due to less precise scores can only really be used in large studies and also provides less information on health status and outcomes than the SF-36.

There have been many previous studies of SF-36 profiles in RA. Ruta and colleagues [Ruta et al. 1998] reported that in 233 patients with RA the SF-36 scales were reliable, correlated with core disease activity measures and were responsive to improvements in health. Birrell and colleagues [Birrell et al. 2000] studied 86 RA patients attending specialist clinics and found that impairment of health status was moderate to marked by the SF-36, with significant differences from population norms and chronic disease states such as low back pain. They concluded that it is a practical tool for use in patients with RA.

1.3.6.2. Nottingham Health Profile

Although the NHP was initially designed as a 2-part questionnaire, only the first part is widely used as part 2 is not applicable to all responders. Part 1 which is commonly used consists of 38 statements which are grouped into 6 subscales; physical mobility, pain, sleep, emotional reaction, social isolation and energy. These statements were generated from large surveys of the general population. Each question has a yes or no answer, each being weighted according to perceived severity. There are a number of problems when using the NHP. Each statement has a simple yes or no question, limiting the subjects' response; the method of weighting the severity of items can give confusing results. There are also problems with floor and ceiling effects, improvements in those with minor ailments who started with a zero score may not be detected, those subjects who score maximally on an item will continue to have the same score despite any deterioration.

There have also been a number of previous studies of the NHP. Houssien and colleagues [Houssien et al. 1997] reported high scores for pain, physical mobility and energy level sections, and also considerable distress levels for sleep and emotional reactions. There were moderate associations between NHP scores and disease activity measures, including the number of tender and swollen joint. Not all studies found an impact on sleep and emotional reaction. For example, Uutela and colleagues [Uutela et al. 2003] evaluated 99 RA patients and found that NHP scores for mobility, pain and energy were very different from control values but sleep, emotional reaction and social isolation were similar between RA patients and controls. The association between abnormal NHP scores and disease activity is shown in all studies and was most recently confirmed by Sivas and colleagues [Sivas et al. 2004], who reported that in 100 RA patients all subgroups of the NHP significantly correlated to pain and the articular index, but not with C-reactive protein levels.

1.3.6.3. EuroQol and Others

In view of new and increasingly expensive treatments for RA, clinical studies often include economic evaluation in the form of cost-utility analysis. In this method a utility is used as a global, health related quality of life measure. A utility being the preference of patients for given states of health. It is expressed as a value between 0 (equal to death) and 1 (equal to full health). Thus, living 1 yr with a utility of 0.5 is equal to living half a year in full health. The three most widely used methods of utility measurement are the standard gamble (SG), the time trade off (TTO), and the VAS. [Sakthong 2008] With the SG, the respondent is asked to make a choice between two options. The first option is the certainty of living with a certain illness for the rest of one's life. The other option is a gamble with two possible outcomes, living for the rest of one's life in perfect health or immediate death. The chances in the gamble are varied to determine the point at which a subject is indifferent about the choice between the certain option and the gamble. The TTO asks the subject to value health states in terms of duration of life in a state of perfect health that would be equivalent to some period with a particular illness such as their own. In large populations, descriptive instruments such as the EuroQol (EQ-5D) are used. [EuroQol 1990; Hurst et al. 1997]

The EuroQol is available in English and many other European languages. It is a validated quality of life questionnaire which has five questions based on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with three levels of answers (no/some/severe problems). From these five questions, descriptive health states were derived and assessed using TTO/SG to create a social tariff.

1.4. QUALITY OF CARE IN RHEUMATOID ARTHRITIS

The focus of patient care, particularly in those people with chronic illness has recently shifted from recording simple outcomes to focusing specifically on the quality of care provided within the National Health Service (NHS) in the UK.

A number of UK national bodies and groups have reported on the components of quality care for people with rheumatoid arthritis (RA). Key recent reports have been published by the NICE [NICE clinical guideline 2009], the National Audit Office [National Audit Office, 2009] and the King's Fund [Stewart et al. 2009]. These built on earlier reports from ARMA [ARMA Standards of Care 2004] and BSR guidelines [Kennedy et al. 2005]. These reports overlap with the new focus on quality care throughout the National Health Service (NHS) [Department of Health 2006] [Darzi 2008].

NICE guidance from 2009 [NICE clinical guidance 79] clearly state that patient centred care should be at the heart of RA management. NICE reviewed many observational and qualitative studies [Bath et al. 1999; Carr et al. 2003; Iaquinata et al. 2004; Jacobi et al. 2004; Kjekken et al. 2006; Neame et al. 2005; Ward et al. 2007; Williams et al. 2007; Wolfe et al. 2007; Barlow et al. 1999; Lempp et al. 2006] and determined that the areas of care most important to patients were knowledge of RA, information about medications, good communication and access to practitioners between appointments. The areas of care that RA patients deemed inadequate were the lack of a multidisciplinary team approach with different team members not having access to their files, lack of care coordination between team members; limited contact with providers of care; lack of continuity of care; lack of social support and to be more involved in treatment decisions.

If true patient centred care is to be established it will be important to identify any barriers that may exist in the current system that prevent this. Deficiencies can be identified using existing standards of care such as ARMA standards of care [ARMA 2004]; these deficiencies may be relevant on a national level but equally may be specific to certain areas. This is best done by engaging with RA patients as well as providers of care using both qualitative and quantitative measures.

1.4.1. Standards of Care

The Arthritis and Musculoskeletal Alliance (ARMA) is a UK umbrella association that brings together a number of organisations that range from patient support groups to national professional bodies and major research organisations in the field of arthritis and other musculoskeletal conditions. At present ARMA has twenty-eight member organisations but is always looking to expand.

The main aims of ARMA are to raise the awareness of arthritis and other musculoskeletal conditions and highlight the need for high quality services in these areas. ARMA also promotes the development of treatment, prevention and rehabilitation. ARMA promotes co-operation, understanding and mutual support between all individuals and organisations concerned with these conditions. In view of its diverse membership it also provides an ideal forum for the exchange of ideas and information.

Although the Department of Health has produced a musculoskeletal framework it is a generic tool for all musculoskeletal conditions and not specific for RA. [Department of Health Musculoskeletal Services Framework 2006]. ARMA, however, has devised and published UK standards of care for a number of conditions. ARMA initially published guidance on inflammatory arthritis, osteoarthritis and back pain. [ARMA standards of care 2004] Since then they have published standards of care for people with connective tissue diseases, metabolic bone disease and regional musculoskeletal pain. [ARMA standards of care 2007]

The standards of care emphasise the key mechanisms, which ensure people with musculoskeletal conditions get the best healthcare possible. They also however,

touch upon some of the other factors that affect people with musculoskeletal conditions such as social support and the effect on their families.

The core aims of the standards of care are to:

- Improve the quality of life for people with musculoskeletal conditions
- Identify the care people with musculoskeletal conditions can expect
- Enable the NHS to improve resource management by preventing avoidable disability, so reducing return GP and hospital appointments
- Promote consistent, evidence-based approaches to advice, prevention and treatment
- Improve productivity and reduce the benefits bill, where appropriate, by supporting people to remain economically active.

The standards of care for people with inflammatory arthritis were devised after consultation with a range of stakeholders, and were welcomed by the Secretary of State. The standards define the services needed across three broad themes.

- *Access to information, support, and knowledge.* The key components are the general promotion of musculoskeletal health, providing guidance on self-management and when to seek advice, and offering information on services, treatments and providers.
- *Access to the right services that enable early diagnosis and treatment.* The key components are early access for diagnosis, the assessment of needs, the use of evidence-based care, preparing individualised care plans, supporting patients to remain in or return to work, and involvement of people with inflammatory arthritis in the development of services for their care.
- *Access to ongoing and responsive treatment and support.* The key components are the presence of multi-disciplinary teams, ensuring patients are involved in self-management, delivering annual specialist reviews, giving continued access to medical care, surgical care and rehabilitation and support.

1.4.2. Measuring Patient Satisfaction

Patient satisfaction has become an important part of the National Health Service (NHS) in the UK. This has been highlighted with the publication the ‘Darzi report –

High Quality for All 2008' which puts quality of care for patients at the heart of new policy for the NHS. Measuring patient satisfaction has been written into GP contracts. Patient satisfaction is affected by every part of the patient pathway, including waiting times, environment and the consultation itself and its outcome. Patient satisfaction can be measured anecdotally or systematically by questionnaires. In order to improve satisfaction, patients' views over a number of specific issues need to be obtained, which is most easily done with multi-item questionnaires. The results of such questionnaires can then be used to develop and improve services, for the benefit of service users.

Many different patient satisfaction questionnaires exist which can be specific, such as measuring satisfaction with a particular treatment or intervention or more general such as the practice accreditation and improvement survey (PAIS) [Greco et al. 2001], which gives an overall view of a practice and its healthcare professionals and is commonly used in general practice. In 1992 Hill et al designed the Leeds Satisfaction Questionnaire which was specifically designed to measure RA patients' satisfaction with outpatient rheumatology services. Tijhuis et al in 2003 designed a patient satisfaction questionnaire for patients with RA receiving outpatient clinical nurse specialist care, inpatient care, or day patient team care.

Leeds Satisfaction Questionnaire

The Leeds Satisfaction Questionnaire was developed to measure satisfaction amongst patients attending a rheumatology outpatient clinic. It is self-administered questionnaire with 45 statements; possible responses are on a 1 to 5 scale ranging from "strongly agree" to "strongly disagree". The domains included in the questionnaire are listed below. Satisfaction with each individual domain can be calculated and also the results can be combined to give an overall measure of satisfaction.

- General satisfaction
- Giving of information
- Empathy with the patient
- Technical quality and competence

- Attitude towards the patient
- Access and continuity

Tijhuis Satisfaction Questionnaire

The Tijhuis satisfaction questionnaire was designed to capture satisfaction with more complex multidisciplinary care that is often provided for RA patients. The questionnaire has 28 items with 8 domains, which were felt to be the most important according to RA patients' perception of quality of care and are listed below.

- Waiting time
- Autonomy
- Continuity
- Efficiency
- Effectiveness
- Knowledge
- Information
- Empathy

1.4.3. The Use of Qualitative Research

Unlike quantitative research which relies on statistics and numbers, qualitative research analyses unstructured information; which can be anything from transcripts of individual interviews to emails and videos. Qualitative research is used to understand people's beliefs, attitudes, behaviours and the reasons behind them. Because of the in depth information that is needed in qualitative research, smaller samples in general are needed compared to quantitative research.

Until the 1970's the term 'qualitative research' was a term used in the study of anthropology or sociology; however, qualitative research is now used in many areas of research including medical and non-medical sciences as well as in the consumer industry and is used to inform business decisions and form policy.

Focus groups and individual interviews are some of the more distinctive and common methods used in collecting data in qualitative research. The focus group technique involves a moderator facilitating a small group discussion between selected individuals on a particular topic. Both individual interviews and focus groups often will have a semi structured interview schedule to include the topics to be discussed.

1.5. RATIONALE FOR RESEARCH

Medical intervention, particularly early intervention, improves the long-term outlook in arthritis [Scottish Intercollegiate Guidelines Network, 2000]. Unfortunately the provision of specialist services and access to modern treatments is uneven with many parts of the UK having limited specialist services; there is also insufficient training for health professionals about the care and support of people with inflammatory arthritis [Scott et al. 1998]. This has consequences for individual patients and for society more widely. Given the costs of inflammatory arthritis to the NHS and to national productivity, it is unfortunate there is no National Service Framework for inflammatory arthritis and other musculoskeletal conditions. This lack of priority status is also reflected in the fact that these conditions are omitted from the Quality and Outcome Frameworks of the General Practitioners' (GPs) General Medical Services (GMS) contracts.

Despite the established and successful “medical model” of care in specialist clinics, many ARMA Standards are not met in Lambeth and Southwark. Partly this is because the Standards highlight aspects of care overlooked in conventional clinical management; for example patients' need for help with work. In addition, they emphasise aspects of health falling outside the traditional scope of specialist clinics. Recent qualitative research by KCL Rheumatology highlighted these issues, including patients' concerns about mobility, fatigue, sleep disturbance and psychosocial difficulties, lack of social support and work related problems. In addition pain remains a problem for many RA patients and has been shown to be linked with general well being, fatigue and disability, despite treatment with

DMARDs [Lee et al. 2011]. Many current clinic attendees use alternative therapies and additional non-prescribed medication as their pain is insufficiently treated.

The principal limitations of the current services seem to comprise: (a) insufficient information for people about inflammatory arthritis and the limited integration of care across the primary-secondary care interface; (b) the lack of focus on outcomes that are important to patients including fatigue and pain (c) the need for individualised care plans that incorporate recommendations over and above the treatment of synovitis.

1.6. AIMS AND OBJECTIVES

The research in this thesis is based on the underlying concept that the clinical outcomes of RA will be improved by adopting a more patient-centred model of care in place of the current medical model, which mainly focuses on minimising the extent and severity of joint inflammation using disease modifying anti-rheumatic drugs (DMARDs). This concept provides a theoretical framework on which the research has been based; it is not a single hypothesis, because it is impractical to devise one or more studies which could test the null hypothesis in a manner suitable for it to be rejected.

Delivering such patient-centred care depends on three critical pieces of knowledge. Firstly, it is important to understand the limitations of current care, and in particular to identify what is not covered in the current approach focusing on controlling joint inflammation. Secondly, it is crucial to explore the key additional assessments, which could be used to extend the current model of care. Finally, it is essential to understand the impact of current care, both in terms of how it has improved outcomes over time and also the way in which clinical decisions about treatment changes to minimise joint inflammation are currently made.

The research therefore principally addresses identifying those strategies which are needed to improve patient centred outcomes in RA. This involves concentrating on the following three inter-related aspects of clinical care:

- a. Firstly, identifying the main current challenges for providing patient-centred care.

- b. Secondly, focusing on patient important outcomes; fatigue and pain. Studies in this area are further subdivided as follows:
- Investigating the assessment of fatigue, a dominant patient-related problem and its associated features in treated RA.
 - Investigating the assessment of pain and the effect of concomitant fibromyalgia in treated RA,
 - Recognising the close interactions between fatigue, pain and fibromyalgic features.
- c. Finally, examining temporal changes in the conventional outcomes of treatment in RA and evaluating the way in which current clinical decisions are made about the treatment of established RA.

The research focuses on the delivery of specialist care within rheumatology units. It does not specifically address alternative models of care, nor does it consider in detail the involvement of general practitioners or other specialist services in the treatment of patients with RA. These associated but important issues lie outside the topics evaluated in this thesis.

1.6.1. Plan of Investigation

The research assesses current clinical care provided in specialist units using quantitative and qualitative methods, investigates patient centred outcomes, particularly fatigue and pain and their effects in RA, and examines the ways in which clinicians make crucial treatment decisions when managing RA.

1.6.1.1. Assessing Current Performance

An initial survey of 100 patients will benchmark adherence to ARMA Standards evaluating the following: promotion of musculoskeletal health, guidance on self-management information on services, early access for diagnosis, full assessment of needs, evidence-based care, individualised care plans, support at work/disability support, involvement of people with arthritis in service development, functioning multi-disciplinary teams, self-management, annual specialist reviews, continuing access to specialist care, and assessment of all medical problems.

Focus groups of patients and healthcare professionals will provide information on what patients want and expect from outpatient services and what limitations and barriers exist that prevent seamless integrated care.

1.6.1.2. Measuring Satisfaction.

Satisfaction will be measured using instruments already designed to measure satisfaction in RA populations such as those developed by Hill [Hill et al. 1992] and by Tjhuis [Tjhuis et al. 2003].

1.6.1.3. Establishing a Local ARMA Framework

PCTs, GPs, allied health professionals (physiotherapists, occupational therapists and podiatrist), psychologists, orthopaedic surgeons and rheumatologists all need to be involved together with patients and their carers. Setting up a local Arthritis and Musculoskeletal Alliance (ARMA) network will enable closer working relationships between all stakeholders involved in RA care and ensure effective local translation of any findings.

1.6.1.4. Focusing On Fatigue and Pain

Current clinical outcome measures, which reflect the requirements of randomised clinical trials for standardised data collection, are too medically focused. From previous studies it is clear that pain, fatigue and disability are important outcome measures for patients [Lempp et al. 2006]. There has been little work looking at the contributors to fatigue in RA and the ways in which disease activity influences RA fatigue has not been investigated to any extent. If fatigue is to be used as an RA outcome measure, it is essential to investigate further its association with other RA outcome measures and it will also be crucial to identify the best assessment instrument; VAS fatigue scores are simple and reproducible; however, multidimensional assessments may provide a more complete picture and improve the understanding of the clinical relationships of fatigue.

Despite substantial improvements in the development of treatments for RA, pain remains a major issue for many RA patients. There has been very little research

looking at chronic pain in RA and its possible contributors including the existence of concomitant fibromyalgia; so-called fibromyalgic RA.

Treatment decisions are now commonly driven by composite disease activity measures, specifically the DAS28 in Europe. However, the DAS28 may be driven by other subjective patient centred outcomes such as pain. Therefore, further work is needed to establish if patient centred outcomes such as pain and fatigue effect disease activity measures and therefore treatment decisions in RA.

CHAPTER 2. PATIENTS AND METHODS

2.1. PATIENTS

2.1.1. General

The studies all evaluated patients with RA who met the 1987 American College of rheumatology Criteria [Arnett FC et al. 1988] and who were attending specialist rheumatology outpatient clinics in South East London, with the exception of the ERAN (Early Rheumatoid Arthritis Network) patients who are from a network of 19 centres across the UK. Due to the ethnic mix within the South East London area a higher proportion of patients with afro-Caribbean and Asian descent were seen compared to other parts of the UK. For example in the studies in South East London the percentage of Caucasian patient ranged between 80-88%, whereas within the ERAN patients the percentage was 96%. In South East London Afro-Caribbean, patients made up 10-15% of patients while 3-7% were Asian; in the ERAN network only 4% were non-Caucasian. The patients included in the study are summarised in Figure 2.1.

2.1.2. Obtaining Patients Views

2.1.2.1. Patient Focus Groups

Both male and female patients were enrolled with early and late disease of differing ages and in different ethnic groups. The appropriate representative number of these patients was estimated from the demographics collected from patients in previous research studies using this population.

Patients were recruited from the rheumatology outpatient clinic at King's College Hospital. Patients were approached via the rheumatology specialist nurses and physicians. The study aimed for six to eight patients in each focus group and six patients agreed to take part in each; there was one drop out in the second focus group.

2.1.2.2. Health Care Professionals Focus Group

Health care professionals who are part of the multidisciplinary team which care for patients with RA were invited to take part. This included a consultant rheumatologist, consultant orthopaedic surgeon (specialist hand surgeon), rheumatology nurse specialist, occupational therapist, physiotherapist and podiatrist.

All health care professionals were involved in the care of patients at King's College Hospital.

2.1.3. Standards of Care and Satisfaction Survey

Prospective data were collected from 100 consecutive patients with RA from specialist rheumatology outpatient clinics at King's College Hospital. Eligible patients were identified from clinic letters of patients attending rheumatology outpatient clinics and blood monitoring appointments.

2.1.4. Fatigue in RA: Patients in Clinical Association Studies

The study looked at two patient groups. The initial clinical association study assessed fatigue using a visual analogue scale (VAS). These patients were attending rheumatology outpatient clinics in one of two hospitals; a large university teaching hospital and a large district general hospital, both located in metropolitan south east London.

All visits entered onto the 'rheumatoid arthritis database' at both hospitals between January 2003 and July 2004 were included. This consisted of 639 clinic visits from a total of 260 patients. For those with multiple clinic visits during this period, only the most recent clinic visit data was used. Of the 260 patients, 22 patients had some data missing from their visit. These visits were therefore not included in the analysis. The data from the remaining 238 patients' visits were analysed.

The second clinical association study (alternative measure study) also used the vitality scale of the SF-36 as an alternative measure of fatigue.

2.1.5. Fatigue in RA: Patients in Treatment Effects Studies

2.1.5.1. Early RA

Data collected from patients enrolled in the early rheumatoid arthritis network (ERAN) were used for the early rheumatoid arthritis study. ERAN is a national network of rheumatologists following outcomes in patients with RA for less than two years at enrolment. There are 19 centres across the UK and Ireland and standardised information is collected on case report forms at first presentation to secondary care,

then again at 3 to 6 months, at 1 year and annually thereafter. The choice and intensity of drug treatment is left to the discretion of the individual centres.

2.1.5.2. Established RA

Data were collected from 54 patients receiving DMARDS and 30 patients receiving anti-TNF therapy in one rheumatology outpatient department in south east London. These patients met the 1987 criteria for RA. Data were collected prior to treatment and after 6 months of DMARD therapy and after 3 months of anti-TNF therapy. Patients who stopped treatment for any reason were excluded.

2.1.6. Fatigue Measurements Study

For the fatigue measurements study, data were collected from 105 patients with RA as defined by the 1987 ACR criteria, who were consecutive attendees in a routine outpatient clinic at King's College Hospital. The sample comprised 80 females and 25 males. Their mean age was 60 years (range 24-88); mean disease duration 13 years (range 0.1-54) and 70% were rheumatoid factor positive. 20 patients were receiving biologics and 78 patients receiving single or combination disease modifying drugs. Their mean DAS28 was 4.53 (SD 1.44) and HAQ 1.49 (SD 0.8).

2.1.7. Initial Fibromyalgic RA and Pain Threshold Study

For the first part of the study to confirm there is evidence of fibromyalgic RA, prospective data were collected from 105 patients with RA as defined by the ACR criteria who were consecutive attendees in a routine outpatient clinic at King's College Hospital.

The sample comprised 80 females and 25 males. Mean age was 60 years and mean disease duration 13 years. The ethnic grouping of patients recruited into the study represented Caucasian, 80%, Afro-Caribbean, 15%, Asian, 3% and Oriental, 2%. At the time of assessment, the majority of patients (93 of 105, 89%) were on second line therapy. Within this group of 93 patients, twenty patients were on biologic therapy, namely adalimumab, etanercept and infliximab. There were 78 patients on single, combination and triple DMARD therapy, which comprised 49 on methotrexate, 21

on sulfasalazine, 7 on hydroxychloroquine, 17 on leflunomide, 1 on IM-gold and 16 on prednisolone. In total 85 patients were either on NSAIDs or analgesics or both.

2.1.8. Replicate Fibromyalgic RA Study (Established RA)

Data collected from patients for a previous study were used in the replicate study. These patients were part of a study to design a patient derived disease activity score. The patients were attending outpatient clinics at four hospitals in South London. The sample comprised 245 females and 76 males. Mean age was 60 years and mean disease duration 9 years. The ethnic grouping of patients recruited into the study represented Caucasian, 88%, Afro-Caribbean, 10%, Asian, 7% and Oriental, 0.6%. At the time of assessment, the majority of patients (244 of 321, 76%) were on second line therapy. Within this group of 244 patients, thirteen patients were on biologic therapy, namely adalimumab, etanercept and infliximab. There were 231 patients on single, combination or triple DMARD therapy, which comprised 151 on methotrexate, 44 on sulphasalazine, 17 on hydroxychloroquine, 12 on leflunomide, 15 on IM-gold, 10 on azathioprine, 9 on ciclosporin, 12 on D-penicillamine and 42 on oral corticosteroids. Thirty patients had been given either intra articular or intramuscular depomedrone. In total 245 patients were either on NSAIDs or analgesics or both.

2.1.9. Fibromyalgic Early RA Study

Data collected from patients enrolled in the early rheumatoid arthritis network (ERAN) were used for the early rheumatoid arthritis study. The sample comprised 265 females and 130 males. Mean age was 55 years (range 18-88). The ethnic grouping of patients recruited into the study represented Caucasian, 96%, others 4%. At initiation into ERAN, 378 patients were on single or combination DMARD therapy, which comprised 17 patients on hydroxychloroquine, 148 on sulfasalazine, 173 on methotrexate, 11 on other monotherapy and 29 on combination DMARDs.

2.1.10. Temporal Changes Study

All patients met the 1987 ACR criteria for RA. They comprised in total 987 patients. Data were collected from five different time points; 1997, 2003, 2006, 2008 and 2010. There were five separate cohorts of patients. All patients were attending

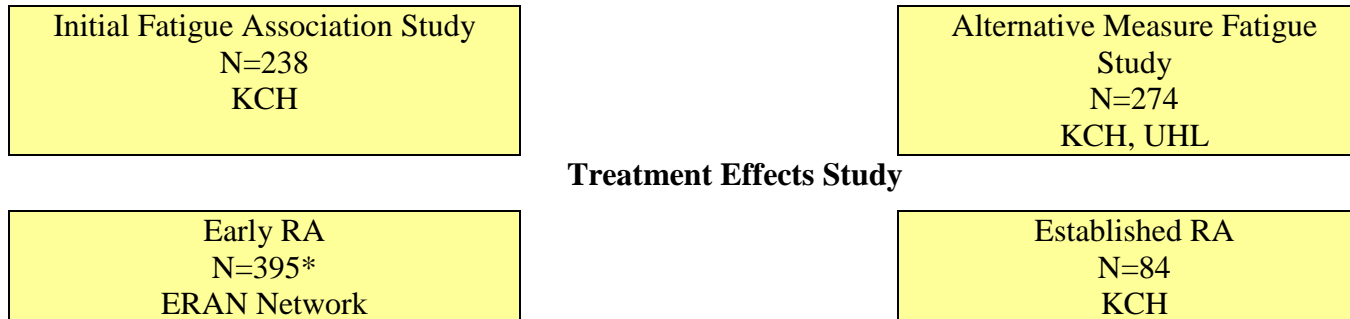
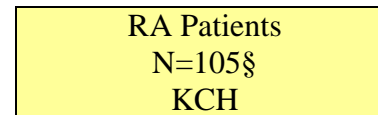
rheumatology outpatient departments from two hospitals within South East London, either a large teaching hospital or a district general hospital. These patients were receiving routine clinical care.

2.1.11. Treatment Changes Study

The patients in the treatment changes study all met the 1987 ACR criteria for RA and were attending outpatient departments in South East London in either a large teaching hospital or a district general hospital. Patients were consecutive attendees at the rheumatology departments in each hospital. This was a cross-sectional study with data collected over a two year span. Patients were receiving routine clinical care.

Figure 2:1 Summary Of Participants' Included In The Study**IDENTIFYING LIMITATIONS OF CURRENT CARE**

RA Patient Focus Group 1 N=6 KCH	RA Patient Focus Group 2 N=5 KCH	Healthcare Professionals Focus Group N=6 KCH and Southwark PCT	
GP Individual Interviews N=13 Lambeth PCT, Southwark PCT, Lewisham PCT	Secondary Care Healthcare Professional Individual Interviews N=15 KCH, UHL, GSTT	RA Patients Individual Interviews N=26 KCH, UHL	Carers N=11 KCH, UHL
Standards of Care Survey and Initial Satisfaction survey (Tijhuis) N=100 KCH		Second Satisfaction Survey (Hill) N=100 KCH	Patient Group Survey N=60 KCH

FATIGUE IN RA**Clinical Association Studies****Fatigue Measurements Study**

FIBROMYALGIC RA AND PAIN THRESHOLDS IN RA

Initial Fibromyalgic RA and Pain Threshold Study N=105§ KCH	Replicate Fibromyalgic RA Study in Established RA N=321 KCH, UHL, GSTT, Woolwich	Replicate Fibromyalgic RA Study in Early RA N=395* ERAN network
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UNDERSTANDING TREATMENT DECISIONS

Temporal Changes Study N=987 (1997 – 202; 2003 – 300; 2006 – 105; 2008 – 71; 2010 – 309) KCH, UHL	Treatment Changes Study N=482 KCH, UHL
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* This represents the same group of patients

§ This represents the same group of patients

KCH – King's College Hospital; UHL – University Hospital Lewisham; GSTT – Guy's and St Thomas's Trust; Woolwich – Woolwich Hospital

ERAN Network – A network of British rheumatology departments who collect & monitor clinical details on all early RA patients in a standard way in order to assess outcome in the long term on a national basis.

2.2. ETHICAL CONSIDERATIONS AND CONSENT

Ethics Research Committee and Research and Development approvals were obtained before the studies began. In accordance with the guidelines of the Ethics Research Committee, all participants received patient information sheets (Appendix) before deciding whether or not to participate in the studies. All patients signed written informed consent forms (Appendix). Patients GPs were also informed of their participation in the research. Although four patients who underwent individual interviews declined to have their GP informed as they felt their GP to have a lack of involvement or interest in their RA care.

Patients were approached within the rheumatology departments of the participating hospitals by a member of the clinical team or the researcher.

2.2.1. Ethics Committee Approval

Ethics Committee Approvals were obtained for each part of the study via the local research ethics committee and were registered with the relevant NHS Research and Development Committees.

2.2.2. Informed Consent

Informed consent was taken from patients participating in each part of the different studies. The forms can be seen in the appendix.

2.3. ASSESSMENTS AND ANALYSES

2.3.1. Qualitative Research in Focus Groups

Qualitative research is used to gain insight into many aspects of people's lives, including their beliefs, concerns and values. Qualitative research has been used in the business world and politically to inform decisions and policy. In medical research qualitative research is often used to gain insight into health beliefs and as well as explore patient experiences. Formal approaches include individual interviews, focus groups, but can also include unstructured materials such as feedback forms. Unlike quantitative research it doesn't rely on statistics or numbers but involves content and discourse analysis.

The audio taped focus groups and 1:1 interviews were carried out in private rooms using a semi structured interview guide [Britten 1995]. The interview schedules were based on related literature [Lempp et al. 2006; Kelly et al. 1996] and the researchers' experiential knowledge. Focus groups and interviews took between one to two hours. Interview and focus group information was transcribed verbatim. Each transcribed text (interview or focus group) was initially loaded into the NVivo Revision computer software [Richards et al. 1999] to manage and organise the volume and complexity of the interviews. This qualitative computer software was used to analyse and handle the data. The data was examined using content analysis [Hsieh et al. 2005] where close attention was paid to what the interviewees reported. Secondly discourse analysis [Hodges et al. 2008] was applied where the language that patients used to describe their experiences was scrutinised e.g. patients trying to please medical and nursing staff, descriptions of self-determination or the impact of RA on their mental health.

The results are presented with verbatim quotations as well as a summary table to highlight the key themes and to help clarify the importance of themes, frequency counts have been added where appropriate. Throughout the data analysis simple counts are made of key themes or issues, this combination of qualitative and quantitative analysis helps assist in the generalisability of the findings. [Seale 1999]. For validation of the data, external qualitative co-researchers, not involved in the data gathering and analysis, cross-checked initial codes and reached agreement with the researchers about the codes for further data analysis. In addition the data were also presented to two experienced clinicians to assess resonance and plausibility with their clinical experiences. To determine the significance for routine clinical practice in an inner city setting, data from all six qualitative studies was studied for relevance in response to the recent publications.

2.3.2. Standards of Care

In contrast to qualitative research, quantitative research is about asking questions in a structured fashion. To get reliable statistical results fairly large numbers of people need to be sampled as opposed to qualitative research where often much smaller

numbers are required. ARMA (the Arthritis and Musculoskeletal Alliance) is the umbrella body for the arthritis community in the UK. It is unique in bringing together over 30 organisations from across the patient, research and professional fields to work to improve the lives of people with arthritis and musculoskeletal conditions in the UK.

The national Standards of Care published by ARMA were developed by patients and health professionals to provide guidelines as to what care patients with inflammatory arthritis should receive. These standards bring together the evidence and best practice and set out a framework for services. The standards and the audit tool were developed by a working group that included representatives from professional bodies such as the British Society for Rheumatology, Royal College of Nursing Rheumatology forum as well as representatives from patient groups such as the National Rheumatoid Arthritis Society. The standards are based on 3 main themes:

- Access to information, support and knowledge that optimise musculoskeletal health and enable self-management.
- Access to the services that enable early assessment and management.
- Access to ongoing and responsive treatment and support.

Patients completed ARMA standards of care audit tool. The full questionnaire can be found in the Appendix. The questionnaire is formed of six main sections and the main themes are summarised in Table 2.1.

Table 2:1 Main Themes of ARMA Standards of Care Audit

Section	Data Items Requested
Section A <i>Your Diagnosis</i>	<ul style="list-style-type: none"> • Type of arthritis • Disease duration • Age
Section B <i>Smoking and Exercise</i>	<ul style="list-style-type: none"> • Smoking status • Smoking cessation advice (if current smoker) • Exercise advice
Section C <i>Inflammatory Arthritis</i>	<ul style="list-style-type: none"> • Suspicion of arthritis-related condition prior to first visit to GP • Pain relief advice at first GP visit
Section D <i>Early Diagnosis and Treatment</i>	<ul style="list-style-type: none"> • Health care professionals seen within first 6 months of diagnosis • Medications offered at first diagnosis • Information offered during first 6 months of diagnosis (written information, information about support organisations, employment and benefits information, teaching and education sessions, details of NHS expert patient programme, helpline number, information about continuing leisure activities) • Opportunities to discuss ongoing concerns
Section E <i>Your Treatment</i>	<ul style="list-style-type: none"> • Involvement in treatment decisions • Written care plans • Service feedback
Section F <i>Ongoing Treatment and Support</i>	<ul style="list-style-type: none"> • Advice when disease flares • GP assessments between outpatient visits (Heart disease, general health) • Regularity of assessments of arthritis by health care professionals • Assessments of interests and emotional needs • Assessment of pain • Support in managing pain (including type of support provided)
Section G <i>Further Comments</i>	<ul style="list-style-type: none"> • Any further comments about multidisciplinary team.

2.3.3. Satisfaction Questionnaires

Initially a satisfaction questionnaire by Tijhuis [Tijhuis et al. 2003] was used. This questionnaire was designed to measure satisfaction with multidisciplinary care. It was designed with the help of patients with RA. It is shown in Appendix. However, patients who completed the questionnaire often found it confusing and difficult to

answer. Therefore a second satisfaction questionnaire by Hill and colleagues was used [Hill J et al. 1992]. This was designed to measure satisfaction of the outpatient care received by patients with RA. It is shown in Appendix. The Hill patient satisfaction questionnaire is self-administered, with patients ticking boxes to indicate their level of agreement with a series of 45 statements. Possible responses are on a 1 to 5 scale ranging from “strongly agree” to “strongly disagree”. This provides a score out of 5 for each aspect of care. Scores above 3 indicate satisfaction and below 3 dissatisfaction. Statements are included on the following aspects of care.

- General satisfaction
- Giving of information
- Empathy with the patient
- Technical quality and competence
- Attitude towards the patient
- Access and continuity

In addition to indicating levels of satisfaction with the above, the results can be combined to provide a measure of overall satisfaction.

2.3.4. Defining the Associations of Fatigue

2.3.4.1. Fatigue Measurements Study

Fatigue was assessed using four specific measures: A double anchored 100mm visual analogue scale (VAS) and three fatigue questionnaires; the FACIT-F [Cella et al. 2003], the MAF [Belza 1995] and the multidimensional fatigue symptom inventory (MFSI) [Stein et al. 1998]. The vitality subscale of the SF-36 questionnaire was also used. All questionnaires were self administered.

The fatigue VAS was labelled at one end ‘no tiredness’, and at the other end ‘absolutely no energy at all’. The question read ‘How tired are you today?’. The range of the scale was 0 (no tiredness) to 100 (absolutely no energy at all).

2.3.4.2. FACIT-F

The FACIT-F is a 13 item questionnaire and scores range from 0-52, it is an inverse scale, the higher the score the less the fatigue. The FACIT-F has four subscales; General fatigue, physical fatigue, mental fatigue and vigour. [Cella et al. 2003]

2.3.4.3. Other Fatigue Scores

The MAF contains 16 items and scores range from 0 (no fatigue) to 50 (severe fatigue). The MAF has four subscales; Severity, distress, degree of interference of daily living and timing. The MFSI includes 30 items and scores range from -24 to 96. The MFSI has five subscales; General fatigue, emotional fatigue, mental fatigue, vigour and physical fatigue.

Anxiety and depression were assessed using the Hospital anxiety and depression scale (HADS). This is a self completed questionnaire which has 14 items; seven items measure anxiety and 7 items measure depression. [Zigmond et al. 1983] Anxiety and depression are measured separately with a range of scores between 0 and 21 for each subscale. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over indicating clinical 'caseness'.

2.3.4.4. Clinical Association Studies

Data analysis was done by the Statistical Package for the Social Sciences (SPSS for Windows 11). Fatigue was analysed in two ways. On the first approach, taking fatigue as a continuous variable, simple linear regression was used to study the individual effects of continuous variables like age, pain, patient global assessment and DAS28. The effects of binary variables were assessed with two sample t-tests.

To determine the key factors that contribute to fatigue in rheumatoid arthritis, simple linear regression was followed by a multiple linear regression model fitted to all the variables in a stepwise manner, paying special attention to multi-collinearities, interactions and potential mediating relationships.

2.3.4.5. Treatment Effects Studies

To assess changes in the SF-36, simple descriptive analyses of baseline data were calculated. Means for all 8 domains of the SF-36 were assessed. To investigate changes over time paired results at baseline and at 12 months were calculated and bivariate correlations and linear regression analyses were undertaken between

different domains. Missing data was imputed using the standard method recommended for SF-36.

To assess the effects of treatment on fatigue two sample independent t-tests and bivariate Spearman's correlations were used.

2.3.4.6. Fatigue Measurement Study

To determine the associations between disability and fatigue simple descriptive analyses (including means and standard deviations) were applied to all the data. Bivariate Spearman's correlations were carried out for each variable against HAQ and each measure of fatigue. Simple linear regression was undertaken; any variable which did not reach significance at this level was not included in any further analysis. Simple regression was followed by stepwise backward multiple regression using HAQ as the dependent variable. In the multiple regression models the DAS28 was used as the measure of disease activity, therefore, tender joint count, swollen joint count, ESR and patient global assessment were not used as the DAS28 is a composite measure of these variables. A multiple regression model for each measure of fatigue was undertaken. Collinearity analysis was carried out for each final model.

2.3.4.7. Factor Analysis

To explore the different dimensions captured in each fatigue questionnaire and also assess their relationship with anxiety and depression, simple descriptive analyses were applied to the data, as well as Spearman's correlations. In this study, correlations of $r \geq 0.6$ are reported as strong correlations, $r \geq 0.4$ and < 0.6 as moderate correlations and $r < 0.4$ as weak correlations. Cronbach's alpha was used to test the internal validity of the items in the fatigue questionnaires. Cronbach's alpha is a coefficient of internal consistency which is commonly used as an estimate of the reliability of a psychometric test. Where validity is concerned with the extent to which an instrument measures what it is intended to measure. [Following this an exploratory factor analysis of the fatigue questionnaires was undertaken. A rotated factor matrix was performed with all the questions from each questionnaire as well as the fatigue VAS and the HADS scores.

In order to identify the most appropriate questions and reduce down the number of items, all items which were not highly correlated were excluded (loading <0.6). To further reduce this both clinical interpretation and statistics were employed to exclude any very similar questions. The questions were examined by the investigator and a second rheumatologist and using clinical judgement and after agreement between the two clinicians if two questions had almost identical wording or it was felt they were asking the same question then the question with the lowest loading was rejected and the question with the highest loading was retained. For example: I feel nervous and I feel tense were felt to be asking the same question. The loading into the factor analysis rotated factor analysis was 0.889 for I feel nervous and 0.672 for I feel tense; therefore, I feel tense was excluded from the final model. Consideration was also made to ensure that each dimension was represented.

2.3.5. Fibromyalgic Rheumatoid Arthritis

2.3.5.1. Initial Study

All analyses used the Statistical Package for the Social Sciences (SPSS® 14 for Windows). Group data was reported using means (standard deviations) and ranges.

The inter relationships between tender points and measures of disease activity were assessed using bivariate Spearman's correlations. To determine the factors influencing tender points, simple regression was followed by backwards stepwise multiple regression using tender points as the dependent variable.

To determine the impact of tender points on patient outcomes, the patients were divided into two groups according to the number of positive tender points used in the diagnosis of fibromyalgia; those with 11 or more positive tender points and those with 10 or less positive tender points.

To determine if tender minus swollen joint counts could identify fibromyalgic RA as accurately as tender points, Receiver Operator Characteristic (ROC) analysis was employed. ROC curve analyses are used in medicine to determine a cut-off value for a clinical test. This is a statistical approach to try and distinguish "normal" from "abnormal". [Altman et al. 1994] The ROC curve is a graph of sensitivity vs.

specificity. Sub-groups were compared using Students t-test and frequencies using the odds ratio.

To assess the factors associated with pain threshold univariate and multivariate Ordinal logistic regression models were performed using STATA version 10 (StataCorp, Texas, 2007). As the distribution of pain thresholds was not linear, they were divided into tertiles for analysis. All continuous measures were entered into the models as continuous variables. For these analyses the crude and adjusted odds ratios with 95% confidence interval are presented, p-values are two-tailed throughout. Any variables that had a p value ≤ 0.05 in the univariate analysis were carried forward into multivariate analysis. Factors showing significant collinearity were excluded from the final model.

2.3.5.2. Replicate Study (Established RA)

To determine if the tender minus swollen joint count formula could identify fibromyalgic RA patients, the formula was applied to data from a group of patients with established disease and they were divided into two groups. The impact of ‘tender minus swollen joints’ was assessed by calculating means with 95% confidence intervals for the outcome measures assessed. To determine the effect of fibromyalgic RA on response to treatment, mean DAS28 scores after 6 months of treatment were compared in the two groups using independent T-test.

2.3.5.3. Early RA Study

To determine if the tender minus swollen joint count formula could identify fibromyalgic RA patients, the formula was applied to data from a group of patients with early disease and they were divided into two groups. The impact of ‘tender minus swollen joints’ was assessed by calculating means with 95% confidence intervals for the outcome measures assessed. To determine the effect of fibromyalgic RA on response to treatment, mean DAS28 scores after 24 months of treatment were compared in the two groups using independent T-test.

2.3.6. Understanding Treatment Decisions in RA

2.3.6.1. Temporal Changes Study

Data analysis was done by the Statistical Package for the Social Sciences (SPSS for Windows 16). Simple descriptive analyses were applied to all data. Mean DAS28 scores with standard deviations and standard errors were calculated for each time period. This was repeated for all the DAS28 constituents (tender joint count, swollen joint count, patient global assessment and ESR). Patients were divided by DAS28 categories into four groups: Remission ($\text{DAS28} < 2.6$), low disease activity ($\text{DAS28} 2.6 \text{ to } < 3.2$), moderate disease activity ($\text{DAS28} 3.2 \text{ to } < 5.1$) and high disease activity ($\text{DAS28} \geq 5.1$). The percentage of patients in each DAS28 category was calculated for each time point. The patients were also grouped into fibromyalgic and non-fibromyalgic RA. Mean DAS28 scores for fibromyalgic and non-fibromyalgic patients were calculated including standard deviation and standard errors.

2.3.6.2. Treatment Changes Study

Data analysis was done by the Statistical Package for the Social Sciences (SPSS for Windows 16). Simple descriptive analyses were applied to all data. Patients were divided by DAS28 categories into four groups: Remission ($\text{DAS28} < 2.6$), low disease activity ($\text{DAS28} 2.6 \text{ to } < 3.2$), moderate disease activity ($\text{DAS28} 3.2 \text{ to } < 5.1$) and high disease activity ($\text{DAS28} \geq 5.1$). For each category the percentage of patients who had a treatment change was calculated. In those with high disease activity ($\text{DAS28} \geq 5.1$) the rate of treatment change was examined further and patients were divided further into five groups according to DAS28. These groups comprised DAS28 of 5.1-5.5, DAS28 of 5.5 to 6.0, DAS28 of 6.0-6.5, DAS28 of 6.5-7.0 and those with a DAS28 of over 7.0. Again percentages of patients who had a treatment change were calculated for each group. The percentage for each type of treatment change was also calculated for each DAS28 category.

To determine what influenced treatment changes binary regression was performed for each variable (univariate analysis) and reported as odds ratios (as there were categorical and continuous variables). Any variable which showed significance ($p \leq 0.05$) at this level was carried forward into the multivariate analysis and the odds ratios are reported. Two models were analysed, firstly DAS28 was used as a measure of disease activity and its constituents were excluded. In the second model the four

constituents of the DAS28 (tender joint count, swollen joint count, ESR and patient global assessment) were included and the DAS28 composite measure was excluded.

Patients were categorised as fibromyalgic and non-fibromyalgic RA (Tender minus swollen joint counts) to explore the effect of fibromyalgic RA on treatment decisions, patients were grouped into fibromyalgic and non-fibromyalgic RA. Chi-squared testing was then used to determine any if there were differences between groups in treatment changes and also the kind of treatment change that was initiated.

To explore the effect of age on treatment decisions, patients were placed into three categories; under 45 years, 45-65 years and over 65 years. The effect of age of onset on treatments decisions was also explored: patients were again placed into three categories depending on age at onset of disease; under 45 years, 45-65 years and over 65 years at onset of disease. Chi-squared testing was then used to determine any if there were differences between groups in treatment changes and also the kind of treatment change that was initiated.

CHAPTER 3. IDENTIFYING LIMITATIONS OF CURRENT CARE

3.1. INTRODUCTION

The focus of patient care, particularly in those people with chronic illness has recently shifted from recording simple outcomes to focusing specifically on the quality of care provided within the National Health Service (NHS) in the UK. To ensure that good quality of care is provided, rheumatologists need to engage with patients and ensure that they are meeting their expectations as well as ensuring that they meet standards set out by nationally recognised organisations such as the National Institute for Health and Clinical Excellence (NICE) as well as more disease specific organisations such as the British Society of Rheumatology (BSR) and the Arthritis and Musculoskeletal Alliance (ARMA).

A number of UK national bodies and groups have reported on the components of quality care for people with rheumatoid arthritis (RA). Key recent reports have been published by the NICE [NICE clinical guideline 2009], the National Audit Office [National Audit Office, 2009] and the King's Fund [Stewart et al. 2009]. These built on earlier reports from ARMA [ARMA Standards of Care 2004] and BSR guidelines [Kennedy et al. 2005]. These reports overlap with the new focus on quality care throughout the National Health Service (NHS) [Department of Health 2006] [Darzi 2008]. It would seem commonsense that long-term disorders like RA require similar seamless integrated care across the primary/secondary interface such as those networks already established for diabetes [Overland et al. 2001].

This study set out to look at what is currently being provided to RA patients in secondary and also primary care. It used both quantitative and qualitative methods. It audited care in an inner city teaching hospital environment against published standards of care devised by ARMA. It also aimed to capture how satisfied patients are with current services by surveying an unselected group of RA patients attending clinics in a London teaching hospital.

Qualitative methods were used to review the services for RA provided in an inner city environment serving an ethnically diverse and relatively deprived population. In a focus group setting patients were interviewed about their experiences in rheumatology outpatients and asked what they feel should be provided. Using

individual interviews as well as focus groups the perceived barriers were assessed that prevent the provision of seamless integrated care across the primary and secondary healthcare sectors. The varying perspectives of patients, carers, specialists and general practitioners (GPs) were examined. Studying such a representative and diverse group of patients, carers and clinicians avoids limitations from concentrating on selected patients and clinical staff linked to national groups.

3.2. OUTLINE OF PATIENTS AND METHODS

3.2.1. Focus Groups

3.2.1.1. Patient Focus Groups

For the focus groups, in order to have diversity and a breadth of views, purposive and quota sampling of patients with RA as defined by the 1987 American college of Rheumatology criteria [Arnett et al. 1988] were undertaken. The aim was to include patients with early disease, late disease, both male and female patients, differing ages and patients in different ethnic groups. Quota sampling using demographic data from a previous study of RA patients in the same population allowed for estimation of the correct number of male patients and ethnic mix in the focus groups.

All patients were recruited from the rheumatology outpatient clinic at King's College Hospital, aiming for six to eight patients in each focus group. Patients were approached either directly by Dr Pollard or by one of the rheumatology nurse specialists. Six patients agreed to take part in each focus group. All patients signed an informed consent (Appendix 1). There was only one dropout in the second focus group, which therefore consisted of five patients. The patient who dropped out was female of Asian background. The demographics for the patients who participated in the focus groups are summarised in Table 3.1.

3.2.1.2. Patient Focus Group Process

The focus group was conducted in a private room at the Weston Education Centre which is contained within the King's College Hospital site. The focus group was recorded using audio equipment. Dr Lempp conducted the focus group as Dr Pollard was the clinician in charge of the care of some of the participants and it was felt that

this may inhibit some discussions. As most participants had not had their comments recorded previously the interviewer tried to establish a relaxed atmosphere and refreshments were provided. The group were informed that they could request that the recording was stopped at anytime and that all comments would remain anonymous. For the focus groups a semi-structured interview schedule was used [Britten 1995]. The content of interview schedule covered three broad topics; Information needs, access to care and outpatient assessment (Appendix 2).

Table 3:1 Patients in Focus Groups

Variable	Focus Group 1 (n=6)	Focus Group 2 (n=5)
<i>Female</i>	5	3
<i>Male</i>	1	2
<i>Age, mean years (range)</i>	58 (45-70)	57 (33-70)
<i>Disease duration, mean years (range)</i>	15 (0.5-32)	9 (1-20)
<i>Ethnicity</i> <i>Caucasian</i>	4	4
<i>Afro-Caribbean</i>	2	1
<i>Asian</i>	0	0

3.2.1.3. Health Care Professionals Focus Group

Health care professionals who are part of the multidisciplinary team which care for patients with RA were invited to take part. This included a consultant rheumatologist, consultant orthopaedic surgeon (specialist hand surgeon), rheumatology nurse specialist, occupational therapist, physiotherapist and podiatrist. All health care professionals were involved in the care of patients at King's College Hospital and signed an informed consent form (Appendix 3)

3.2.1.4. Health Care Professional Focus Group Process

The focus group was conducted in a private room at the Weston Education Centre which is contained within the King's College Hospital site. The focus group was recorded using audio equipment. Dr Pollard conducted the focus group with the help of Dr Lempp. The group were informed that they could request that the recording was stopped at anytime and that all comments would remain anonymous. For the focus groups a semi-structured interview schedule was used [Britten 1995]. The content of the interview schedule covered three broad topics; interaction between

primary and secondary care, interaction of the multidisciplinary team and outpatient assessment (Appendix 4).

3.2.1.5. Focus Groups Data Analysis

Data were drawn from each focus group. Each focus group was transcribed verbatim and loaded into NVivo 8 computer software to manage and organise the transcripts. A three stage structured approach as described by Fisher [Fisher, 1999] was followed: (1) managing the data, (2) reading the data and (3) building categories or themes.

Data were examined through content analysis by paying close attention to what the interviewees in each focus group reported. Discourse analysis [Tonkiss 1998; Potter 1997] was also applied. This meant that language was not only considered as a means of communicating information or stories, but also as a medium from which knowledge can be built. Applying both categories in the data analysis is an approach endorsed by Silverman [Silverman 1993] and Seale [Seale 1998].

To increase the clarity of the results, they are presented in the form of verbatim quotations, as well as by summary of key themes along with frequency counts where appropriate. Throughout the data analysis the occurrence of key events is noted by using simple counts. This approach assists in the generalisability of the findings [Seale 1999]. Such methods can aid validation and credibility of qualitative work [Seale 1999; Silverman 1993; Bryman 1988].

3.2.2. Perceived Barriers to Integrated Care in RA

Focus groups and face to face interviews held between 2005-8 involved 79 participants working in or attending three hospitals and three primary care trusts (PCTs). These groups comprised:

a. Two patient focus groups: As described above a purposive sample of 11 RA patients was obtained from one hospital outpatient department; their selection was stratified by disease duration, gender, ethnicity and age. They comprised 8 females and 3 males with a mean age of 58 years and mean disease duration of 12 years;

eight were Caucasian and three from black and ethnic groups. One patient refused to take part.

b. Patient interviews: Data from a previous qualitative study of individual interviews with 26 RA patients from two outpatient clinics was re-analysed to determine what patients want and expect from primary and secondary care. This study was part of a Total Quality Management (TQM) Project. The aim of the study was to explore patient's experience of living with RA and their views about primary and secondary care [Lempp et al. 2006].

A quota sample of 26 patients was obtained from the same hospital as the focus group participants and one other hospital outpatient department to reflect socio-demographic characteristics and duration of illness of the two RA clinics' population. They comprised 22 females and 4 males of mean age 56 years and mean disease duration ten years; 18 were Caucasian and eight from ethnically diverse groups. There was no overlap in the patients between the individual interviews and focus groups. Nine patients refused to take part.

c. Carers interviews: the carers consisted of a convenience sample of 11 carers from two hospital outpatient departments. They were approached by staff and the researcher through the RA patients they were caring for. They included five females and six males of mean age 61 years; seven were Caucasian and four from other ethnic groups.

d. Specialist Health Care Professionals focus group: As described above, six representative members of one multidisciplinary team participated, consisting of consultant rheumatologist, consultant orthopaedic surgeon, rheumatology nurse specialist and allied health professionals (occupational therapist, physiotherapist and podiatrist).

e. Specialist Health Care Professionals interviews: 15 secondary care specialist staff (6 consultants, 4 specialist registrars and 5 rheumatology nurse specialists) from three hospitals. Eight declined participation in the study.

f. Generalist Health Care professional interviews: Data from a previous qualitative study of individual interviews with 13 GPs from three Primary Care Trusts (PCTs) were re-analysed to determine the role GPs feel they have in the management of RA. The two aims of the interview study were to obtain the views and perceptions of local general practitioners about the quality of care they provide for RA, the quality of the interface between primary and secondary care for RA and also how they see their role in delivering care to patients with long term chronic illness.

The decision to use previous data from individual GP interviews was twofold. Firstly, GPs work as individual practitioners so to get a better feel for the GPs perceived role in RA management views from multiple GPs is preferable rather than having one GP in the focus group. Secondly, recruitment for the GP individual interview study had proven very difficult and only 12 out of 99 GP surgeries approached agreed to take part and recruitment had taken 9 months. The strengths of using this approach is that we have included GP data in our study and this enables us to have looked at all stakeholders involved in RA care without having to have spent 9 months trying to complete just this part of the study. The individual interviews were also in depth and allowed for exploration of different practices. The weakness of using this approach is that it did not allow us to ask the specific questions that were relevant to this study and it is possible that there were other themes that were not captured in the available data.

All patients met the American College of Rheumatology 1987 criteria for RA. Socio-demographic details of patients who were interviewed individually and carers are summarised in Table 3.2. Written consent was obtained from each participant and each study was fully approved by the relevant local Research Ethics and Research and Development committees.

Table 3:2. Individual Interview Patients and Carers

	Individual Interviews (<i>n</i> =26)	Carers (<i>n</i> =11)
<i>Female</i>	22	5
<i>Male</i>	4	6
<i>Age, mean years (range)</i>	56 (25-85)	61 (36-74)
<i>Disease duration, mean years (range)</i>	10 (1-29)	N/A
<i>Ethnicity</i>		
<i>Caucasian</i>	18	7
<i>Afro-Caribbean</i>	7	3
<i>Asian</i>	1	1

3.2.2.1. Perceived Barriers to Integrated Care in RA: Data Analysis

The audio taped focus groups and 1:1 interviews were carried out in private rooms using a semi structured interview guide [Britten 1995]. The interview schedules were based on related literature [Lempp et al. 2006; Kelly et al. 1996] and the researchers' experiential knowledge. Focus groups and interviews took between one to two hours.

Interview and focus group information was transcribed verbatim. Qualitative computer software NVivo 8 was used to analyse and handle the data. Content and discourse analysis were applied [Hsieh et al. 2005; Hodges et al. 2008], including single counting [Seale 1999] and deviant results [Seale 1999]. For validation of the data, external qualitative co-researchers, not involved in the data gathering and analysis, cross-checked initial codes and reached agreement with the researchers about the codes for further data analysis. In addition the data were also presented to two experienced clinicians to assess resonance and plausibility with their clinical experiences. To determine the significance for routine clinical practice in an inner city setting, data from all six qualitative studies was examined for relevance in response to recent publications.

3.2.3. Standards of Care and Satisfaction Survey

For the standards of care and satisfaction survey, prospective data was collected from 100 patients with RA. All men and women with a diagnosis of RA according to the 1987 ACR criteria attending outpatient clinics at King's College Hospital were

eligible to take part. Eligible patients were identified from clinic letters of patients attending rheumatology outpatient clinics and blood monitoring appointments in the outpatient department at King's College Hospital.

These patients were then approached by Dr Pollard whilst in the rheumatology department at King's College Hospital and invited to complete the ARMA standards of care audit tool and the Tijhuis satisfaction questionnaire [Tijhuis et al. 2003] with respect to the care they have received at King's College Hospital.

A second satisfaction survey was undertaken following the collection of the Tijhuis questionnaire as various comments were received from patients regarding problems with understanding the questionnaire which was used. The second satisfaction survey [Hill 1992] was completed again by 100 patients with RA as defined by the ACR criteria who were consecutive attendees in a routine outpatient clinic at King's College Hospital. The questionnaires were completed anonymously in order to gain candid views of the outpatient services provided. Therefore no demographic data is available for the patients who completed the standards of care or satisfaction questionnaires.

3.2.3.1. Standards of Care Questionnaire

The ARMA standards of care for inflammatory arthritis audit tool is an anonymous, confidential, multi-part, self completed questionnaire. The audit tool was designed by ARMA. The full questionnaire can be found in the Appendix. (Appendix 5)

3.2.3.1.1. Data Analysis

Simple descriptive analyses were applied to the main data in all groups. As the treatment of RA has changed over the last few years with greater emphasis on multidisciplinary care and improved therapies, patients with early disease (as defined by disease duration of less than two years) were grouped together and the results for section D (early diagnosis and treatment) were analysed separately with simple descriptive analyses.

3.2.3.2. Satisfaction Questionnaires

The Tijhuis satisfaction questionnaire [Tijhuis et al. 2003] was trialled initially; which was designed to measure satisfaction with multidisciplinary care. The questionnaire was designed with the help of patients with RA and in the study was used to compare satisfaction between inpatient and outpatient multidisciplinary care. (Appendix 6) However, after speaking to patients who completed the questionnaire, many found it confusing and difficult to answer. Therefore a second satisfaction questionnaire by Hill [Hill et al. 1992] was trialled. This was designed to measure satisfaction with the outpatient care received by patients with RA. The initial ten patients who completed this questionnaire found it easy, simple and quick to complete. (Appendix 7) The Hill patient satisfaction questionnaire is self-administered, with patients ticking boxes to indicate their level of agreement with a series of 45 statements. Possible responses are on a 1 to 5 scale ranging from “strongly agree” to “strongly disagree”. This provides a score out of 5 for each aspect of care. Scores above 3 indicate satisfaction and below 3 dissatisfaction. Statements are included on the following aspects of care.

- General satisfaction
- Giving of information
- Empathy with the patient
- Technical quality and competence
- Attitude towards the patient
- Access and continuity

In addition to indicating levels of satisfaction with the above, the results can be combined to provide a measure of overall satisfaction.

3.3. RESULTS

3.3.1. Clinical-User Group

Louise Pollard was the convenor of the Lambeth and Southwark ARMA local network and members include a consultant rheumatologist and an orthopaedic consultant as well as specialist nurses from rheumatology at King’s College Hospital.

The allied health care professionals in musculoskeletal health are represented by podiatrists from Southwark and physiotherapists and occupational therapists from King's College Hospital. Southwark Primary Care Trust (PCT) is represented and a number of patients sit on the steering committee. These include patients with inflammatory arthritis, who are cared for at King's College Hospital, a representative from the National Rheumatoid Arthritis Society (NRAS) and the chair of the patients' forum for primary care in Southwark.

The network was used as a springboard to identify areas which could be improved within the local provision of services for people with musculoskeletal disorders. The audit against ARMA standards of care once completed was presented at a local network meeting. Several points were highlighted as areas on which the network can work. These include; improving access to information, particularly regarding benefits and patient groups, improving referrals to appropriate exercise programmes, ensuring timely assessments and review by allied health care professional (physiotherapists, occupational therapists and podiatrists) and also to ensure that patients are regularly assessed for other co-morbidities.

In the first meeting the patient representatives highlighted the lack of a patient support group for patients attending King's College Hospital, therefore a survey of patients with inflammatory arthritis attending King's College Hospital rheumatology department was undertaken, to assess the need for a local patient support group. (Appendix 8)

3.3.2. Patient Support Group Survey

A simple self-completed questionnaire was designed by Catherine Morrison (rheumatology specialist nurse and local network member) and Louise Pollard. Patients were asked if they thought setting up a support group was worthwhile and if so how often should the group meet and where. Patients were also asked whether they themselves would attend and if they would be involved in setting up and running the group. The full questionnaire can be found in the Appendix. (Appendix 8)

The total number of respondents was 60. The majority of patients felt setting up a patient support group was a good idea (85%) and 65% of patients stated that they would attend meetings, however, only 43.6% of patients would be willing to help set up and run the support group. With regards to the timings of such meetings, the majority (66.7%) were in favour of three-monthly meetings and just over half the patients felt they should take place in the mornings with 84.6% of patients feeling that the meetings should be held at King's College Hospital (Table 3.4).

Table 3:3 Patient Support Group Survey

	Responses (n=60)		
Is patient support group good idea?	Yes 51 (85%)	No 9 (15%)	
Would you attend group?	Yes 39 (65%)	No 21 (35%)	
Interested in setting up/running group?	Yes 17 (43.6%)	No 20 (51.3%) [§]	
How often should they be?	Monthly 26 (66.7%)	3 Monthly 12 (30.8%)	Other 1 (2.6%)
What time of day is best?	AM 20 (51.3%)	PM 16 (41%)	Evening 3 (7.7%)
Where should it be held?	KCH* 33 (84.6%)	Elsewhere 5 (12.8%) [‡]	

[§] 2 Non-responders

* King's College Hospital

[‡] 1 patient ticked both boxes.

3.3.3. Focus Group Results

3.3.3.1. Analytic framework

An analytical framework emerged from the data from both focus group transcripts and three overarching themes became apparent. The three broad themes and their related sub-themes are described below.

Theme 1: This theme refers to the *personal impact of RA* on the body and mind and the related adjustments following the diagnosis of RA.

Theme 2: This theme describes the *information needs* of RA patients, related to RA and its treatment and the services and benefits available as well as how to access the information.

Theme 3: This theme documents specific issues related to *health care delivery* for RA patients.

Theme 1: Personal Impact of RA

Within this first theme, four specific subthemes were identified:

- Coping Strategies
- Signs, symptoms and diagnosis of RA
- The impact of RA on the body and mind.
- The impact of RA on everyday life and family.

Theme 2: Information needs

Within the second theme, three specific subthemes were identified:

- Information about RA and its treatment
- Information about social services and benefits available
- Delivery of Information

Theme 3: Health Service Delivery

Within the final third theme, four specific subthemes were identified:

- Access to care
- Relationships with medical staff
- Organisational issues
- Expectations of care

In the following presentation of the results, each participant's direct account will be shown in quote brackets in italics and will be preceded by a study identification code (e.g. A2 = Second patient to speak in the first focus group, B5 = Fifth patient to speak in the second focus group). Any words that are underlined were emphasised by a participant to give them added importance during the focus group discussion. If any

quote needs clarification, an explanation will follow the quote in question within square brackets [] and are my own words rather than those of the participant. Patients' actions such as laughter will also be placed within square brackets in the text. The strength of any particular topic will be indicated by how many participants made a similar point, for example, the majority of patients (7/11), means that 7 participants made comments about a specific topic out of the total number of RA patients who took part in the focus groups.

3.3.3.2. Theme 1: The Personal Impact of RA.

Although the participants were not asked specifically to describe how they were diagnosed with RA or its impact upon them, most patients discussed (9/11) their symptoms, how they coped with their illness (7/11) and the impact RA has on their body and life in the private domain (7/11) as well as the impact on their body and life which is seen in the public domain (5/11).

Coping Strategies

Patients described using a variety of strategies to cope with the signs and symptoms of RA. These included, taking to their bed in times of flare (2/11), exercising/keeping active/distracting themselves (4/11), taking comfort in the fact that others are worse off (2/11), changing their diet (2/11). There was a common theme through many patients accounts of accepting that they had to get on with it and 'grin and bear' the pain and disability and not be beaten by rheumatoid arthritis. (6/11)

A3: 'I think if you, if you're having a bad day and you're feeling a bit down and you go out and you see someone who's in a lot worse condition than you are, you look at these people and you say to yourself: "there for the grace of god go I, so buck yourself up and get on with it". And that makes you feel a lot different...it lifts your own spirits and shakes you out of the doldrums because there are a lot of people that are a lot worse off than we are...'

A5: 'everyone finds different ways to manage themselves. Everybody, there's no separate set of fast rules. You have to know what works for you. And this is the method in which I work, never mind what anybody else doing, I will do what makes

me tick and if I find walking around the room, doing unnecessary dusting make me feel better, I will do that.'

B3: 'I went into the homeopathic hospital for 2 weeks for them to analyse me...and I was put on a wheat free diet at one stage which I wasn't allergic to but I didn't need it in excess. I then was on a dairy diet, the same applied, I mean everything's different but I don't think now the diets [that] helped but they helped me with my pain, they didn't get rid of the swellings or you know the rheumatoid factor but certainly they helped with the pain.'

B3: 'You know I think it's the personality of people with rheumatoid that we grin and bear it. We don't ring up and say "help I've had the most terrible week or night or whatever it is, please I need to see somebody". Generally, you don't, you just get on with it don't you?'

B5: 'That's what I do when I'm struggling to do something, they're all like "let me help you" and I'm like "no", you know let me give it my all and then if....and only if, will I let someone help me.'

Signs, Symptoms and Diagnosis of RA

Almost all patients (10/11) discussed the signs, symptoms and diagnosis of RA. Several patients talked about the pain they endure from their RA (4/11) and the impact it has upon them, especially sleep (4/11) some describe the pain as sufficient to make them cry (3/11). Although not specifically asked many patients discussed their initial presentation, how they were diagnosed and their initial referral (7/11). Several patients reported being diagnosed quickly after their first consultation with their GP (3/11) but one patient described a lengthy delay in diagnosis and referral (1/11)

A2: 'that pain makes me cry, especially when I try to sleep and I can't sleep because if I lie on this side I'm in pain, if I lie on that side, you don't know where to go'

B1: 'I'm getting pain in my hands for the last two years and it is absolutely indescribable pain and I have it all night long, I can't sleep and actually I'm not embarrassed to say it but I sit there crying, the pain is so severe'

B2: 'My own doctor sent me directly here (rheumatology clinic).'

B5: 'I used to tog to the gym so it took my GP nearly a year and a half to find out I had RA and it was only because I demanded an x-ray....the GP kept telling me it was poor ligaments and that I should stop going to the gym and rest.'

The Impact of RA on the Body and Mind

The majority of patients (6/11) described the effect RA has on their body and mind. Many patients (5/11) discussed how RA interferes with their ability to carry out what they would have previously considered to be normal daily activities. Two patients (2/11) specifically discussed the impact RA had on their ability to work.

Several patients (4/11) described the emotional impact of RA and two patients (2/11) described how their inability to perform certain physical tasks in front of others added to their emotional load.

A1: 'but then at the end it got, you know, lifting you can't do the job and you've got to say "I can't do it [nursing task]". I was very upset about it [not being able to carry out all the nursing duties].'

A2: 'I could hardly open my hands at one time; I couldn't pull anything down or tighten anything. Sometimes when I went shopping I had to put the bag over that side to carry it, my hands could hold nothing.'

A3: 'Because you get a lot of emotional problems with it as well and a hell of a lot of emotional problems with RA.'

B4: 'Or when you're working, you can't even hold your pen properly and you write scrawly, you know it's very debilitating but also as well I mean that's what the emotional aspect comes into it.'

The Impact of RA on Everyday Life and Family

Patients (4/11) discussed the impact RA has on their everyday life and family. Three patients (3/11) talked about the negative impact RA had on their ability to work, with

two patients (2/11) specifically describing how they felt their diagnosis would impede their ability to gain employment.

Several patients (3/11) described their embarrassment at work and in public situations because of the limitations caused by RA. Another theme discussed (4/11) was the apparent lack of understanding by not only work colleagues but also by members of family. Patients felt that people could not understand the limitations caused by RA.

A3: 'even family members don't understand. When they sort of, oh well, especially when you first start off and you can't do things like, even just opening a jar or something like that and you ask someone: "oh you can do that" you know. But you can't do it and I mean my brother used to say to me: "oh do this, do that" and I'd say: "but I can't do it". "Of course you can do it", you know, and they just don't understand how you're struggling.'

A5: 'nobody understands, nobody knows what you're talking about and they're [colleagues] not willing to understand, not because probably they're heartless but: "look I am a company boss and I want my job, my work done, so you just do it". So it really is difficult when you're at work, when you're still at working age and have this, this illness [RA]. So you just have to say it [disclose the diagnosis] very carefully.'

B5: 'That's the scary thing with me being made redundant I've kind of had to lie to my new employer and say that my RA is under control and my RA isn't.'

'My boyfriend will take me out for a romantic meal and I'll be sitting there while he's cutting my dinner up for me in a restaurant, how embarrassing is that (laughs).'

3.3.3.3. Theme 2: Information Needs of RA Patients

Information about RA was important to many patients (6/11) and they accessed this information in different ways. When discussing social services and benefits, the majority of patients told of their difficulty accessing any help (7/11). Patients talked about different delivery systems for information and from the data it is clear that no one method is suitable for all patients.

Information about RA and Its Treatment

Most patients were as keen for as much information about RA as possible (6/11) and some mentioned that RA was not something they were aware of before being diagnosed (3/11). Almost half of patients (5/11) relied on medical staff for the majority of information, whereas some utilised other professionals such as pharmacists (3/11) for further information particularly about drugs. The leaflets available in clinic were found to be beneficial for some patients (5/11). A considerable number of patients gained useful information from fellow RA patients (5/11).

A1: 'Yeah you have to find out. I asked... I think word of mouth you find out a lot to be honest. You get, people saying "oh I get this" and you go "where, how did you get that?" And they tell [other people] you.'

B2: 'So you do need to talk to you, know an expert who tells you what you might be getting or what you might not be getting or if you do get this. I mean that's why the pamphlets are so good... '

B3: 'The other person who's helped me is my chemist because he's got the list of all the drugs I'm on and he knows. So if I've got a cold or something I can go into him and say "can I take this with all that I'm on?". I mean that's helping on that side of it, he will say yes well that you can take not that.'

B4: 'because I had not heard of rheumatoid arthritis when I was diagnosed'

Information about Social Services and Benefits Available

On the whole patients talked negatively about their experiences with accessing social services and benefits, including how to contact them and many (7/11) discussed how difficult they were to access and how difficult the forms are to complete. A minority of patients had benefits in place already (3/11).

A3: 'I mean I think it's still very hard to get registered as disabled unless you've got the physical attributes to see. But when you see people who've lost limbs and things and not being registered disabled, you think to yourself: "well what chance have I

got". I mean when I've come to renew my disabled driving badge I very much doubt if I'll get it [the badge] this time because I don't look as bad as I did before.'

B1: 'I think the information available is so limited. It ahm... leaves you in the dark you know, exactly where you are and what benefits you can get.'

B2: 'I had experience of someone coming from social services coming and spending two hours in my home and they kept repeatedly telling me that I wasn't entitled to benefits which would consist of going through all the motions, the paperwork, the history and everything else...'

Delivery of Information

Patients had different ways of accessing information, some preferred using the internet (4/11); however two patients mentioned not having a computer and not being computer literate. Some patients still preferred information leaflets and felt they should be in plain, understandable English (3/11). One patient mentioned the expert patient programme but the other patients in that focus group were not aware of it. One patient talked very positively about a group they had attended at King's college hospital where they had several sessions with input from physiotherapy, occupational therapy, rheumatology specialist nurses/doctors, fellow patients as well as someone from social services who explained what benefits were available and how to access them. The other patients in this focus group felt that they would have benefited from attending but had never heard of it/been offered to attend. However, one patient mentioned that they would prefer not to attend a group and preferred being given information one to one.

B1: 'Beef up you leaflets...'

B2: 'In plain understandable English...'

B3: 'The trouble with all these big groups, I'm not really a big group person, you know. Where if having somebody come to my house to talk me through something is one to one rather than being a whole group set up where you're just a number and

.... it's.... and it's not really what you need, you only need that bit of information, rather than listen to a whole talk.'

B4: 'I did go at that time to some self help groups that were arranged through occupational therapy [OH] here and found out more through that about what I could do to help myself, things like that and the rest of the information through the internet going on the internet and finding out information from there... Well when I was actually diagnosed in 2001 the hospital had some kind of group that we were coming to and the lady there she was really good, she said "you can apply for benefits" you know, "do this, get occupational Therapy to come in and assess you at home" and everything like that.'

3.3.3.4. Theme 3: Health Care Delivery for RA Patients

Access to care

Most patients (6/11) commented that it was important to have immediate access to care in times of need such as a flare of disease, although this could prove difficult.

Some patients used their relationships with specialist nurses to gain access to doctors (2/11), whereas others used a helpline number (2/11), although some patients were not aware of the helpline (4/11).

A4: 'And you've got their number (nurses), you can ring them.'

A3: 'So you've got that fluidity there if you feel you need to see the doctor. You can always phone up the nurse and they'll help you to get to see the doctor quicker than you would if you just try to change your appointment and fetch it [appointment] forward. If you say you've got a problem...'

B4: 'I continuously phoned, continuously phoned ... and I got through to Cathy to find out that they're trying a new system but we weren't told. No-one was told as you said. So you know, when I came up ahm... she said "oh well this person only works two afternoons part time". That's not helpful when you want help, you want to see someone, you know. Sometimes its a phone call because you can't physically get there you know, in the end that's what I had to do, physically come to clinic because I couldn't get anyone on the phone.'

Relationships with Medical Staff

Patients talked very positively about their relationships with medical staff, particularly specialist nurses (9/11). They clearly described a different relationship with nurses compared to doctors (9/11) and felt more able to talk freely to nurses and patients felt the nurses understood them better. Some criticisms of rheumatologists were that some patients (5/11) felt their appointments were rushed, some (3/11) felt that the doctors were not interested in them. A few patients (3/11) mentioned that continuity of care was important as it allowed them to build up a relationship with their doctors. Some patients (3/11) criticised their GPs apparent lack of knowledge of RA, whereas some patients (2/11) had very little to do with their GPs and relied on the rheumatology department for the majority of their care. Two patients did describe a good relationship with their GPs.

A1: 'Mind you I find it quite easy to talk to the specialists. I've got to know the specialist quite well. I think I've seen him so many years, you do get to know them and they get to know you.'

B1: 'The nurses are all hands on...it doesn't bother me if I never have an appointment with the [rheumatologist] or any of them, it doesn't bother me what so ever. It's the nurses...if I see the nurses I'm quite happy and I see them every week because you can guarantee they're there. You can guarantee they're not going to phone you up or send you a letter we can't be here this week or something like that you know. But I find that especially with the [rheumatologist]'

B3: 'I do think you need a good nurse (agreement from rest of group). They're your first port of call (agreement from rest of group) and if they understand you first and that you're not exactly.... and they can see all your results and so they know you, what you're talking about...'

B4: 'You're lucky if you get 10 minutes [with the rheumatologist]; I mean again if you're working, you have to leave work early, you know to get here. Sometimes that's another thing, when you see the waiting time is horrific and you go in and you're talking to the rheumatologist, he's not even looking at you, so you're talking to him sideways..'

Organisational Issues

Several criticisms involving organisational issues were mentioned by patients; two patients complained about waiting times for blood monitoring in the hospital whereas more (3/11) were concerned that blood monitoring was going to be handed over to primary care. Other issues included long waiting times to be seen in rheumatology clinic (2/11) and repeated cancellations of appointments (2/11). Two patients also mentioned the problems with lack of interaction between primary and secondary care.

B2: Your problem with the postponing of appointments, I had three postponed; three appointments and I told them I wasn't happy. Three appointments and I said "This is the third one you know"... I was pushed to the side.

B3: 'Here is a nightmare; you can be here an hour and a half and none of us have that much time...you have not got an hour and a half, to sit and wait to have your bloods taken...'

Expectations of Care

Some patients clearly relied heavily on care provided by nurses but when seen by rheumatologists, patients (4/11) discussed the need to be examined thoroughly and for doctors to have a sympathetic approach. Patients also wanted to feel as if they are being listened to (2/11).

A3: 'It would be nice if they did automatic joint checks for you. I mean I know the nurses do at times when you're having TNF but the doctors don't tend to, not unless you've got a problem.'

B1: 'Especially if it's a period of time like 6 months [for an appointment with the rheumatologist], you know that's a long time. If you're up every week, I don't think you're going to drastically change, you know, but if it's every 6 months, they should give you a thorough examination, send you for x-rays or god knows what, just to see how you're coping.'

B3: 'Acknowledgement actually, sympathy [from the rheumatologist]'

3.3.4. Perceived Barriers to Integrated Care in RA

Through detailed examination of all the data three main barriers to high quality care were identified. These comprised (i) delayed specialist referral; (ii) limitations to routine follow up and (iii) accessing care in times of need. Examples of matters raised by patients, carers and healthcare professionals are summarised in Table 3.5

Specialist Referral

Patients and Carers

Most patients (29/37) consulted their GPs when their symptoms started. Many (14/37) reported frustration at delays in specialist referral; only one patient commented on being referred early. Some patients (4/37) reported specialist referrals depended on positive blood tests, two of these patients had been diagnosed within the previous twelve months. Delayed referral was mentioned by two carers (2/11).

Healthcare Professionals

All rheumatology specialists in the focus group (3/3) commented on delayed referrals, noting variations in the timing and quality of referrals. This issue did not feature in interviews with individual specialists. Some GPs (4/13) emphasised the need for early referral but many (11/13) commonly waited for ‘positive blood tests’ for rheumatoid factor before referring. Some GPs (5/13) also waited for confirmatory responses to initial treatment with anti-inflammatory drugs and steroids. A number of GPs (5/13) were influenced by their perceived role as ‘gate keepers’ to specialist care.

Limitations in Follow Up

Patients and Carers

Many patients (18/37) commented on the importance of monitoring their RA, highlighting the need for physical examinations together with explanations of disease progress and joint discussion of options of new treatments. They wanted the opportunity to participate in decisions about their care. Patients (12/37) focussed on the value of understanding approaches by staff and developing trusting relationship over time with nurses and doctors.

Some patients (8/37) commented critically about insufficient time during consultations with rheumatologists. By contrast there were many positive comments about interactions with rheumatology nurses (32/37). Patients felt more comfortable discussing matters with specialist nurses, who both understood their concerns and had more time (7/37).

Patients reported organisational problems including long waiting times in clinic (13/37), blood sampling for disease modifying anti-rheumatic drugs (DMARDs) monitoring (9/37), between appointments (5/37) and clinic cancellations and postponements (2/37).

They described mixed experiences with their GPs. On the one hand many (21/37) expressed criticisms about GPs' perceived lack of knowledge of RA and its up-to-date treatment (9/37). On the other hand a substantial number of patients reported positive experience in primary care (14/37), often mentioning sympathetic ongoing relationships (8/37). A minority preferred to receive most care in hospital (6/37).

Carers also voiced concerns about waiting times in the clinic (5/11), perceived limited benefits from treatment (4/11) and difficulties with transport to the clinic (3/11). One carer was concerned about GPs limited knowledge. Most (6/11) commented on the importance of good interactions with outpatient clinic staff. Carers noted that RA had major impacts on themselves as well as on the patients they were caring for.

Healthcare Professionals

Specialists' views (16/18) echoed patients' experiences about the paucity of follow up appointments and lack of time during consultations; they found it difficult to adopt a holistic approach with patients. They noted that these pressures had resulted in appointments with rheumatologists being replaced by specialist nurse led clinics.

Most GPs (10/13) commented on their role in providing repeat prescriptions after the initial referral of patients with RA, otherwise they are only marginally involved in

ongoing care. Only a minority (4/13) reported they regularly reviewed patients with RA.

Few GPs (4/13) commented on the negative impact of the Quality and Outcomes Framework (QOF). They stated it influenced their approach to chronic disease management and, as RA falls outside this framework, they thought it reduced the priority given to RA patients in primary care.

Access to Care in Times of Need

Patients and Carers

Patients emphasised the importance of immediate help and support during times of flare of their RA and/or emotional stress (14/37). They tend to approach rheumatology nurses first to gain access to specialists during flare ups. Carers did not comment on this topic.

Healthcare Professionals

Most specialists (11/18) agreed that patients need immediate access during an exacerbation of RA and that the service should respond quickly and effectively. However, such access increased pressure on appointments leading to overbooked clinics and long waiting times.

Most GPs (8/13) considered an important pre-requisite for accessing secondary care was having a personal relationship with the consultant(s) and having knowledge about him or her. These professional links helped access to specialists during acute episodes of RA (9/13). When such links did not exist (4/13) it limited successful primary/secondary care integration. One GP thought this relationship was hindered by the 'choose and book' system as patients might be seen in hospitals unfamiliar to them. (Choose and Book is a national electronic referral service which gives patients a choice of place, date and time for their first outpatient appointment in a hospital or clinic.)

Table 3:4 Summary of Key Themes

Barriers	Non-Professional		Professional	
	<i>Patients</i>	<i>Carers</i>	<i>Secondary Care Specialists</i>	<i>General Practitioners</i>
<i>Specialist Referral</i>	<ul style="list-style-type: none"> • Delay in referral from primary care 	<ul style="list-style-type: none"> • Delay in referral from primary care 	<ul style="list-style-type: none"> • Delay in referral from primary care • Quality of referral influences prioritisation 	<ul style="list-style-type: none"> • Role as gatekeepers to specialist care • Need for positive blood tests • Referral linked to personal confidence and role perception
<i>Routine follow up and DMARD monitoring</i>	<ul style="list-style-type: none"> • Lack of time with rheumatologist • Cancellation and postponement of appointments • Perceived lack of knowledge of GPs • Poor primary/secondary care interaction 	<ul style="list-style-type: none"> • Waiting times in clinic • Transport difficulties • Perceived lack of knowledge of GPs • Poor primary/secondary care interaction 	<ul style="list-style-type: none"> • Time pressures • Paucity of follow up appointments • Lack of monitoring by GPs 	<ul style="list-style-type: none"> • Lack of regular review • Lack of clarity of role in monitoring
<i>Access to care in times of need</i>	<ul style="list-style-type: none"> • Difficulty of access during a flare 	<ul style="list-style-type: none"> • No specific comments 	<ul style="list-style-type: none"> • Seeing patients urgently impeded by time pressures and paucity of appointments. • GPs not providing emergency care 	<ul style="list-style-type: none"> • Lack of knowledge of RA treatment • Preference for personal knowledge of rheumatologist to access secondary care urgently

Quotations Exemplifying Issues in Specific Areas of Care

Area	Patient/Carer	HealthCare Professional
<i>Specialist Referral</i>	<p>I was diagnosed really soon because I put on a lot of weight and at the time I was on a tablet to stop smoking. I thought it was the tabletsI went straight to the GP and he carried out the rheumatoid blood tests. So I was diagnosed pretty early so I felt quite lucky. (Patient 32)</p> <p>‘I used to go to the gym so it took my GP nearly a year and a half to find out that I had RA and it was only because I demanded an x-ray... (Patient 37)</p>	<p>‘If they think it’s an inflammatory arthropathy, most GPs will send it to the appropriate people, maybe not quickly enough.’ (Consultant Orthopaedic Surgeon)</p> <p>‘So initial diagnosis is key and quick referral putting the right things in the letter so that when we get the letter we can see what they [GP] think it is...there’s huge variation then in that.’ (Consultant Rheumatologist)</p> <p>‘If you don’t do the blood test the hospital would be <u>absolutely</u> overwhelmed. If everybody [patient] who thought they might have rheumatoid we refer to hospital, the system would grind to a halt... (GP1).</p> <p>‘So we normally do blood tests like RA Factor and antibodies and when they come back and yes the suspicion is that they might have RA, then we refer’ (GP2).</p>
<i>Routine follow up</i>	<p>‘Especially if it’s a period of time like 6 months [between appointments], you know that’s a long time...they should give you a thorough examination, send you for x-rays or god knows what, just to see how you’re coping.’ (Patient 33)</p> <p>‘He tries to help me; he is a really understanding doctor. He understands how I feel. I can really talk to him. He knows how I feel. I tell him where I am having the pain. I relate to him.’ (Patient 22)</p> <p>‘I have to wait a long while to see the doctor when I got an appointment for a certain time. I have waited one hour and a half; you never go in at the appointment time’. (Patient 15)</p> <p>‘I think sometimes the specialists haven’t got the time to</p>	<p>‘It depends what they come in with. You don’t always have time.... I mean if they have everything at once it’s really difficult to address every issue in that time slot. ‘(Nurse Specialist)</p> <p>‘I think the follow-up in rheumatoid has changed a bit in the last of couple of years from our perspective in that with the pressure on follow up slots being so great, the interval between follow-ups is much longer and it will be pushed out to 6 months or a year’ (Consultant Rheumatologist)</p> <p>‘I’d like the GPs to take on blood monitoring, I think that is a complete waste of time for us to look at each single blood result for 100 of 100 of patients and so I would like to have blood monitoring with our support to be out in the community. Patients would prefer that as well’.</p>

	<p>give you that long chat that you need, whereas the nurse will. You know, not that the specialist doesn't want to...' (Patient 31)</p> <p>'My GP, I have... I think I have lost respect...he hasn't really served me particularly well. I have to 'play act' when I see a GP. So I have to pretend that I am really ill and about to die before anything actually happens ... I don't have a lot of faith in them'. (Patient 24)</p> <p>'Well my GPs quite good. If it wasn't for my GP half the things he told [advised] me what to do. If you come to the hospital, you ask how you do this, nobody tells you.' (Patient 30)</p> <p>"In the end I got so mad with them (GP) I started shouting and I said "you know, I've got to come up here and ask you for blood forms every month!"(Carer 8)</p> <p>'Doctors... I think they get tired of me (carer) when I attend the consultation.' (Carer 5)</p> <p>'I mean obviously the waiting times can get on your nerves.' (Carer 11)</p>	<p>(Rheumatology Specialist Registrar)</p> <p>'... so we sort of monitor them [RA patients] from the practice... just doing their bloods, seeing everything is in order and there is no sort of active flare up or anything and we are happy to do that if we get a sort of proper protocol and guidelines in which we can work' (GP 10).</p> <p>'.... there is no financial incentive and actually I don't agree with the financial incentive, but if you suffer from an illness that is not included in the QOF, I think there is a degree of neglect and ahm... there is no motivation of the practice to think about that [RA]' (GP 4).</p>
<i>Access to care in times of need</i>	<p>'If the nurse thinks I am not all that good, she calls the doctor... and he will come and see me right away' (Patient 1)</p>	<p>'.....I like the patients to have better support...seeing someone in six months...is not very helpful...they [patients] just struggle on... I have no follow up appointments...the GPs don't know what to do you see, so it is a dreadful situation... we are under-resourced. I don't think that is the way to deliver it [health care]... knowing that we can't actually do that [provide emergency cover]'. (Consultant Rheumatologist)</p> <p>'Patients can now 'choose and book' any hospital which is extremely confusing for GPs, because I think it is extremely important that the patients go to local hospitals and I am familiar with the consultants and the system there.' (GP 9).</p>

3.3.5. Standards of Care

Of the 100 respondents; 95 patients stated they had RA. Ninety-six patients gave information about disease duration; 84 patients had a disease duration of greater than 2 years and 12 had the disease for less than 2 years. The mean age of respondents was 56 years. On first presentation to the GP with symptoms of inflammatory arthritis only 26 of 94 respondents (27.7%) of patients actually thought they had an inflammatory arthritis. However, 61 of the 90 respondents (67.8%) were given advice regarding pain control at their first visit.

3.3.5.1. ARMA Standards

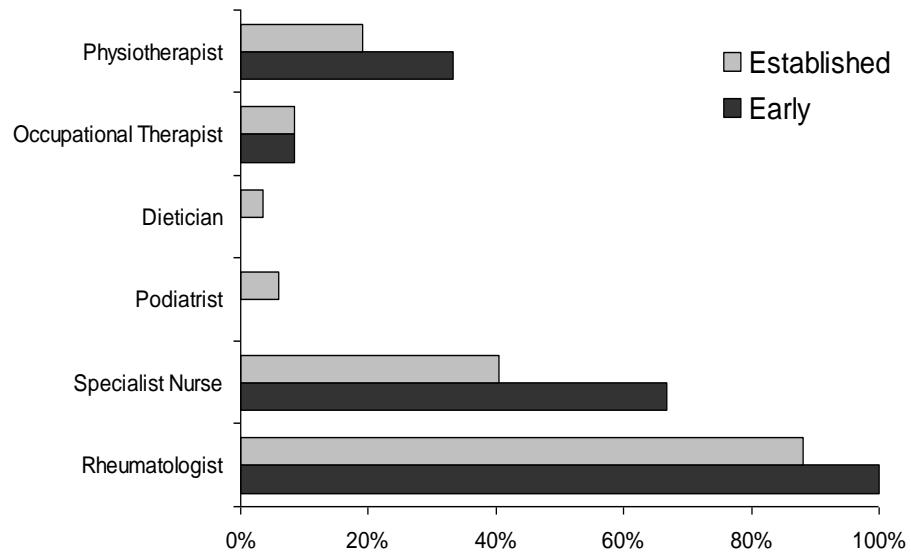
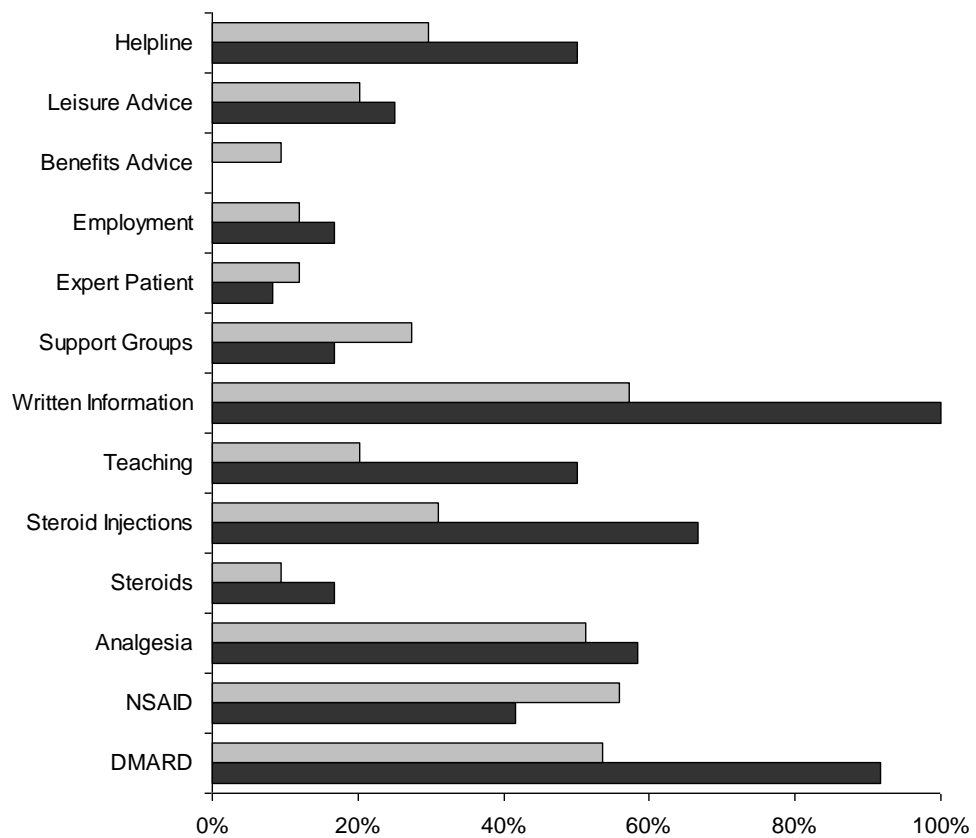
Early Diagnosis and Treatment

Patients were asked to answer questions about the treatment they received during the first six months after diagnosis. A total of 88 of the 100 respondents had seen a rheumatologist within six months of diagnosis, 43 had seen a nurse specialist, 5 had seen a podiatrist, 20 had seen a physiotherapist, 8 had seen an occupational therapist and only 3 had seen a dietician (Figure 3.1).

When looking at those patients with early disease, defined as those with a disease duration of less than two years, all 12 patients had seen a rheumatologist within six months of diagnosis and 8 patients (66.7%) had seen a nurse specialist. However, only 4 patients (33.3%) had seen a physiotherapist, 1 patient (8.3%) had seen an occupational therapist and no one reported seeing a podiatrist or dietician within the first six months of diagnosis.

At first diagnosis, 58 of the 100 respondents were offered a disease modifying anti-rheumatic drug (DMARD), 56 patients were offered anti-inflammatories, half (50 patients) were offered analgesics, 10 patients were offered oral steroid tablets and 35 patients were offered a steroid injection (Figure 3.2).

Again looking at patients with early disease a greater proportion were offered a DMARD; 11 patients (91.7%), 5 patients (41.7%) were offered anti-inflammatories, 7 patients (58.3%) were offered analgesics, 2 patients (16.7%) were offered oral steroid tablets and 8 (66.7%) patients were offered a steroid injection.

Figure 3:1 Early Involvement: Access to Professional Advice**Figure 3:2 Early Involvement: Range of Care Provided**

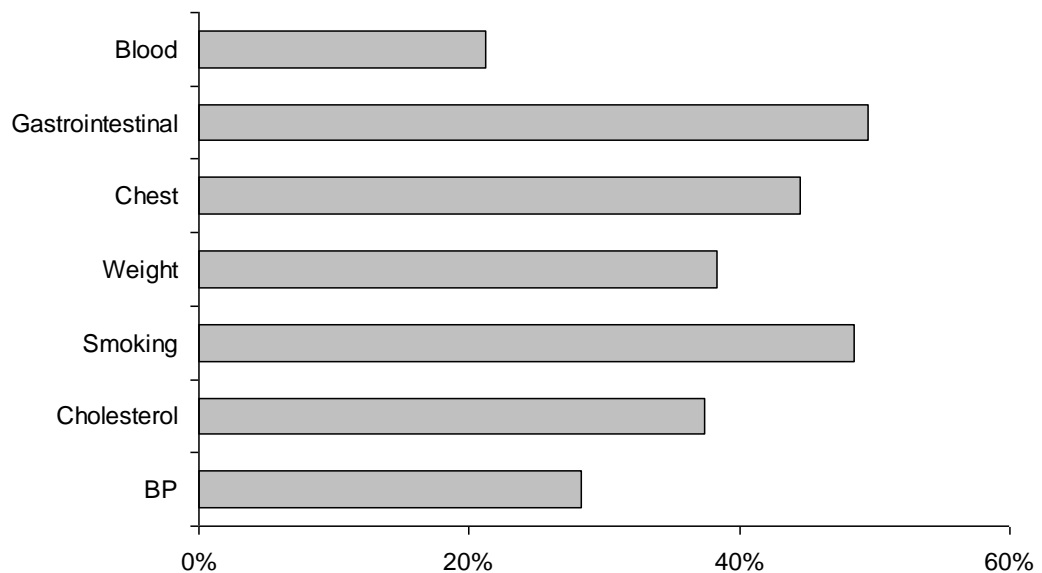
Finally patients were asked if they were given the opportunity to discuss ongoing concerns at visits. Of the 88 respondents, 73 patients (83%) felt they were given an opportunity to discuss ongoing concerns and 15 patients (17%) felt they were not given an opportunity.

Ongoing Treatment and Support

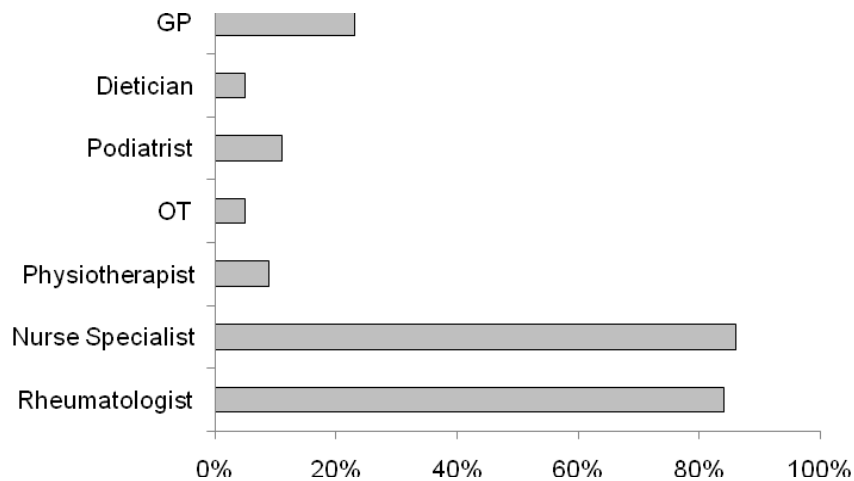
The care patients receive from their GPs/practice nurses between visits to the rheumatology department is summarised in Figure 3.3.

Despite the known increased cardiovascular risk in RA patients relatively few have their BP monitored.

Figure 3:3 Integrated Management of Care: Treatments Offered



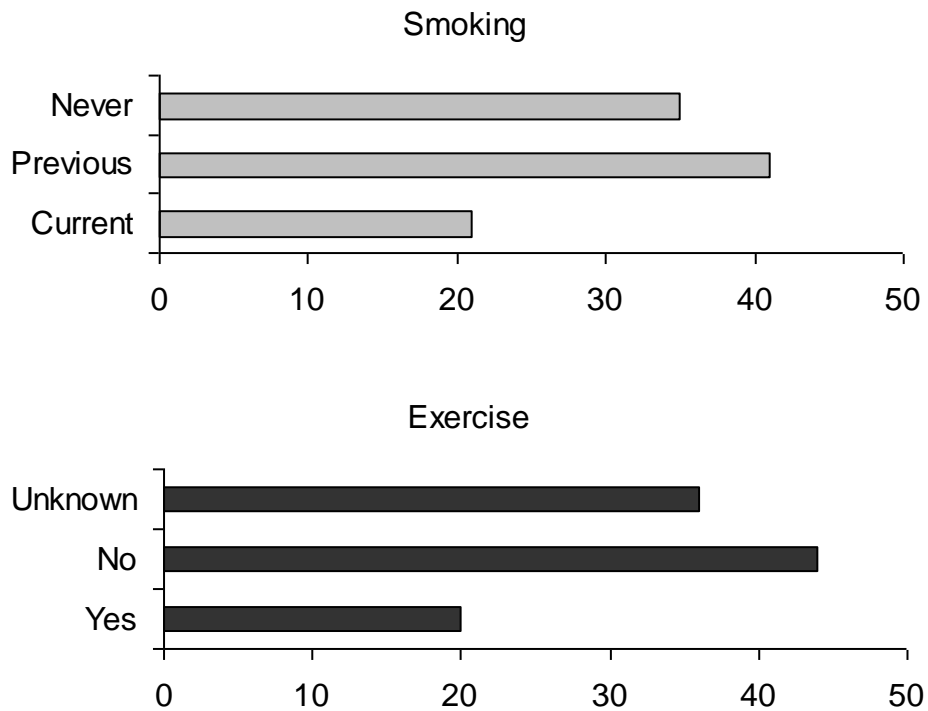
Patients were asked how often their arthritis is assessed by the different healthcare professionals (annually, more often, less often, never, don't know). The majority of patients have their arthritis assessed annually or more often by both rheumatologists and specialist nurses, but rarely by other healthcare professionals. The results are summarised in Figure 3.4.

Figure 3:4 Annual Assessments by Healthcare Professionals

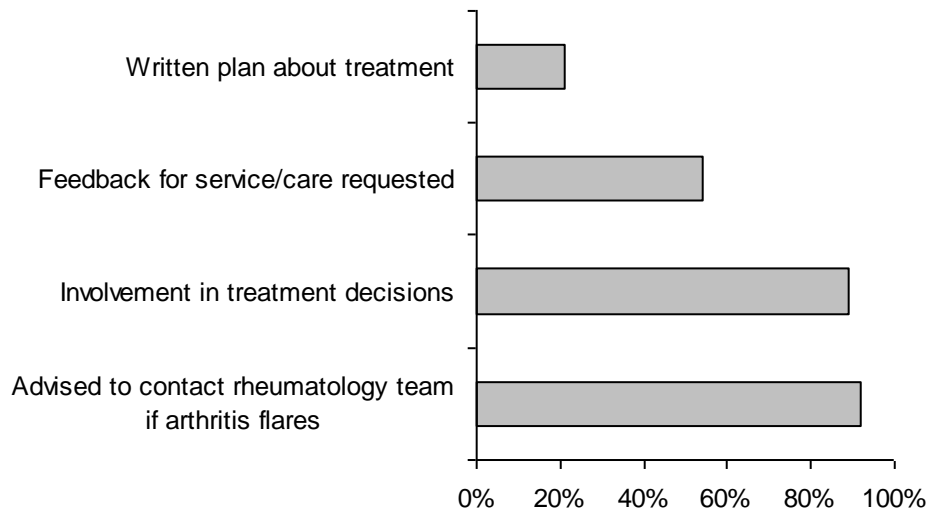
Smoking and Exercise

Ninety-seven patients answered the question relating to smoking status; 35 patients had never smoked, 21 patients were current smokers and 41 patients were ex-smokers. A total of 14 (66.7%) of the 21 current smokers had been offered advice about how to give up, 1 patient didn't answer the question. (Figure 3.5)

Sixty-four patients responded to the question: Have you been offered advice about exercise programmes run at (or recommended by) the hospital? Of the 64 respondents only 20 patients (31.25%) had been offered advice (Figure 3.5).

Figure 3:5 Smoking And Exercise**Involvement in Treatment**

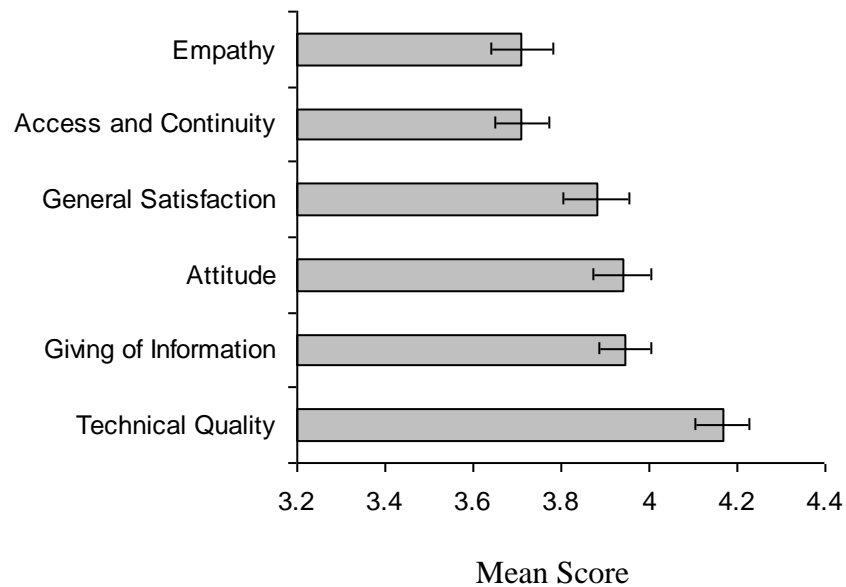
Eighty-six patients (88.7%) felt that they have been involved in decisions about their treatment but only 19 patients (21.3%) have been given written care plans. Fifty patients (54.3%) had already been asked to provide feedback on the service and care they receive. Eighty-seven patients (91.6%) have been advised to contact the rheumatology team should their arthritis flare or become worse (Figure 3.6).

Figure 3:6 Involvement in Care

3.3.5.2. Satisfaction with Care

Hill Satisfaction Questionnaire

Patients were asked to give their overall opinion of the care they received in the rheumatology outpatients department. An overall satisfaction score was calculated for each patient as well as a mean and median for the whole group. One hundred patients completed the satisfaction questionnaire. The lowest score possible is 1 with a maximum of 5, the higher the number the greater the satisfaction. Scores above 3 indicate satisfaction and below 3 indicate dissatisfaction. The mean scores and standard deviations for each subgroup are summarised in Figure 3.7. The mean score in each subcategory was above three, indicating satisfaction with the care provided. The mean scores were fairly similar across each subcategory; empathy with the patient and access and continuity having the lowest mean scores at 3.71 and technical quality and competence being rated highest at 4.17. The overall mean satisfaction score was 3.89 (range 2.08 - 4.92).

Figure 3:7 Hill Satisfaction Questionnaire

3.4. DISCUSSION

3.4.1. Standards of Care and Patient Satisfaction

The standards of care audit in our population of patient shows that care is satisfactory in some areas but there are many aspects of care in which improvement is needed to meet ARMA standards. The majority of patients are seen and assessed frequently by rheumatologists and specialist nurses, and most patients have been offered written information about RA but clinicians are particularly poor at giving information about benefits and this most likely reflects the fact that nurse specialists and doctors often know very little about this subject themselves. The fact that all patients with early disease (less than 2 years) had been seen by a rheumatologist within six months of diagnosis would suggest an improvement in recognising inflammatory arthritis in primary care and an appreciation that patients should be referred early. The majority of patients feel they have been involved in decisions about their treatment but the majority have not been given written care plans. Clinicians are offering advice about cessation of smoking to over two thirds of smokers but less than a third had been offered advice about exercise programmes.

In the last few years the focus of treatment in RA has changed to early aggressive treatment, with better treatments available and the department has also developed closer working relationships with occupational therapist and podiatrists. However, despite these changes only a third of patients with early disease had seen the physiotherapists, less than 10% reported seeing an occupational therapist and no-one reported seeing a podiatrist within six months of diagnosis. There may be some confusion about the terms OT and podiatrist which may account for the greater number claiming to have seen a physiotherapist, but even so, the numbers are small. One other possible explanation is recall bias and also in those with longstanding RA asking patients to recall events within the first 6 months of diagnosis has inherent difficulties.

Most patients know to contact the rheumatology department should they experience a flare of their arthritis. However, between outpatients visits, although GPs frequently ask about blood tests, other possible signs and symptoms of co-morbidities are not being checked. One possible explanation for these findings is a lack of communication between primary and secondary care as rheumatologists often feel that management of blood pressure and cholesterol for example should be done by the GPs, but the GPs often think that this being undertaken in the rheumatology department as the patients are being seen frequently in secondary care. Another possible explanation of these findings is patient recall. This may also represent a lack of recognition by GPs of the association between RA and cardiovascular disease. [Bell et al. 2011]

These findings suggest that for patients in south east London an integrated care pathway would be ideal which ensures that patients receive the information they require, as well as ensuring they are referred on appropriately to other health care professionals and ensuring that patients are screened for other co-morbidities and finally bridging the gap between primary and secondary care.

Setting up the Lambeth and Southwark ARMA local network has been an important step. The ARMA network has brought together patients and the different stakeholders within secondary care who look after people with RA and has facilitated new important relationships. The ARMA network may also help to bridge the gap

between primary and secondary care and has already engaged with podiatry which is a primary care based specialty.

Despite the shortfalls in the service provided as shown by the ARMA standards of care audit, patients overall are satisfied with the care they are receiving. The overall satisfaction was rated at 3.89. The possible range is 1-5 and any score over 3 is considered to show satisfaction. Technical quality scored highest (4.17) suggesting that patients feel that their doctors are competent, however, empathy scored lowest (3.71) suggesting there is some way to go in addressing all of the patients concerns. This has been born out to a degree in the qualitative work which shows that patients often feel that nurses address issues that doctors do not, such as exploring emotional issues and the effect on their everyday lives that doctors often do not enquire about. Although having a more empathic attitude towards patients may improve satisfaction rates, it may also be that it is important for patients to see both specialist nurses as well as doctors as there is no doubt that they often provide help with different aspects of the disease and that clinicians should be assessing satisfaction with the service as a whole and not just the service as provided by doctors or nurses.

3.4.2. Focus Groups: Defining Patients Needs

This qualitative study identified three key areas of importance to our RA patients and their needs. These are; the personal impact of RA, information needs, and health care delivery. The study aimed at looking at the needs of RA patients with regards to outpatient care. Despite the remit and the semi structured interview schedule patients talked quite extensively about the effect of RA on themselves and their everyday lives. They described vividly the pain they suffer as well as the emotional toll RA has on them. There was also a feeling of lack of understanding from work colleagues but also from members of their own families. These issues in some way mirror some of the findings in the satisfaction survey which showed that patients were least satisfied with the empathic attitude of doctors. It is important to understand and address patients' emotional needs as well as physical needs. Rheumatology specialist nurses may be best placed to address these issues.

Despite the fact that most RA patients report that they had been given written information about RA in this study, most wanted more information about RA and its treatment. It seems that there is not a universal medium for delivery with which everyone is in agreement. While many prefer to use the internet to access their information not all are computer literate or have computers. Some patients prefer group meetings while others are put off by this suggestion. Although it is clear that clinicians need to provide more robust information about RA and its treatments, this will need to be provided in a variety of formats. Another aspect which was mentioned by the patients which was also picked up on the ARMA standards of care audit was the lack of information on social services and benefits. As stated previously this is likely due to the fact that doctors and nurse themselves may have little knowledge of these areas. Clearly further information about the services and benefits available at both a national and local level need to be provided.

Most rheumatologists will agree that patients with RA should have immediate access in times of a flare of disease and this is something that patients felt strongly about, but they also commented on the difficulty of achieving this. Some patients use the relationship they have developed with specialist nurses to gain access to rheumatologists in times of need whereas a considerable number of patients will just 'grin and bear it'. It is important that patients do have access when needed and although a helpline number exists for these patients only a few knew about it. Patients need to be informed and reminded of how to access care between appointments should they experience a flare of disease and this access needs to be reliable so that they will use it appropriately. Relationships between staff and patients are clearly important and patients in this study described their relationships with specialist nurses more fondly. Continuity of care is important for patients as is being given time in an appointment and having an understanding and sympathetic attitude. Patients dislike waiting for long periods to be seen and then for the appointment to be rushed. These considerations need to be taken into account when designing follow up clinics for RA patients, this will not necessarily be easy given the pressures on appointments but by ensuring that patients are seen by both specialist nurses and doctors will in some way alleviate this. Rheumatologists however, still need to appreciate that patients need to be given time to address their problems which may not just be related to their joints.

3.4.3. Perceived Barriers to Integrated Care in RA

This qualitative study identified three key areas in which there were perceived barriers to seamless integrated care in RA from the perspective of patients, carers, specialists and GPs. These are early referral, limitations of ongoing care for established RA and management of acute flares. The study took place during a period in which NICE guidelines and other UK care strategies were being developed, and therefore helps place the findings in context. The results are relevant as there are few multi-perspective studies in rheumatology [Chard et al. 2002] and the multiperspective qualitative approach is very useful to capture the experiences of all stakeholders involved in the treatment and care [Kendall et al. 2009; Worth et al. 2009; Black et al. 2009; Exley et al. 2005].

This qualitative study was conducted in three out-patient clinics and three PCTs consisting of 79 participants of whom 37 were patients. It is difficult to assess how generalisable the findings of this study are, although patients were selected from two different clinics. The question over whether the emerging themes are general ones or merely represent local issues is difficult to answer although evidence from previous studies would suggest that similar issues occur more widely, examples include previous studies which showed delays in referral caused by the presence or absence of positive blood results [Suter et al. 2006; Robinson et al. 2010], the need for good access and working relationships with specialists [Bernatsky et al. 2010] and the lack of experience/knowledge of the primary care physician [Jacobi et al, 2004]. The lack of time with rheumatologists and lack of communication between primary and secondary care has also been noted in other parts of the world [Bernatsky et al. 2010].

Qualitative approaches allow patients to give first-hand accounts of their experiences, in this case their experience of the care provided in primary and secondary settings. By focusing on detailed descriptions and their meaning, such in-depth accounts, from semi-structured interviews, may uncover aspects that cannot be readily captured by structured questionnaires and provide information that is helpful

when trying to re-organise services. To date little research has addressed the views of all stakeholders involved in the care of RA patients.

Delay in referral, highlighted in the present study, has also been suggested in previous guidelines and observational studies from the UK [National Audit Office, 2009; Steward et al. 2009] and Europe [Raza et al. 2011]. Experience with both the Norfolk Arthritis Register [Harrison et al. 2000] and the Steroids in Very Early Arthritis trial [Verstappen et al. 2010] have shown that it is possible to see UK patients with inflammatory arthritis in the early stages of their disease. The possible causes of delay in referral are complex and there may be several explanations, such as reflecting organisational aspects; however, alternate explanations may include patient issues such as the disparity between actual observed and perceived time to referral in those patients with long disease duration, who may find it difficult to accurately estimate any delays after such long periods. Patients may also take some time to identify their symptoms and hence achieve referral, which may be reflected in a perceived delay in referral. Finally it is not certain if many patients present with features that could be interpreted as leading to rheumatoid arthritis but, over time, melt away and do not progress. Other publications have suggested that people with inflammatory arthritis delay seeking medical advice [National Audit Office 2009] which could also impact on the time to referral to secondary care. In particular previous studies have shown that ethnicity may play a part in the delay in people seeking help [Kumar et al. 2010] as well as their willingness to accept aggressive treatment [Constantinescu et al. 2009]; these observations are pertinent given the multicultural population served by South London. However, the issue of people delaying seeking help was not discussed by patients or GPs. One clear message from research with GPs was that they are concerned about their role as “gatekeepers” to secondary care. This potentially creates reluctance to refer patients with possible inflammatory arthritis for specialist advice and is a barrier that needs to be removed.

There are several limitations in the ongoing management of established RA that could be overcome by changes in the arrangements of the service. One major issue is insufficient time in secondary care appointments so that clinicians do not fully address major concerns for patients. The greater involvement of specialist nurses has been particularly helpful [Tijhuis et al. 2003], but is not enough by itself. The

evidence suggests that specialists should devote more time and resources to the follow up of patients with established RA [Lempp et al. 2006]. The NHS Musculoskeletal Framework should assist this goal by transferring stable musculoskeletal disorders to community based units and allowing specialists to focus on managing RA. This will require a re-evaluation of new to follow-up ratios as low ratios, often considered a mark of effective care, may actually indicate poor quality care in RA.

A second important issue is the limited knowledge many GPs have about RA [Stewart et al. 2009; Bernatsky et al. 2010; Jacobi et al. 2004]. This reflects not only the absence of musculoskeletal disorders from the Quality and Outcomes Framework but also the dearth of rheumatology teaching in the postgraduate training of UK GPs [National Audit Office 2009]. Whilst some GPs provide high quality care, this is by no means universal [Stewart et al, 2009]. It is impractical to equip all GPs with enough expertise to make significant inputs into the management of RA patients, and the best solution may be to make better use of those GPs with particular expertise in the field. This has been utilised in some parts of the country by the establishment of so-called GPSIs (GPs' with a specialist interest). Many of these GPs could be trained within rheumatology departments running clinics alongside consultants gaining greater insight and knowledge, which can then be transferred into the community setting.

The final key issue is the need for close collaboration between primary and secondary care. Terminology may hinder improvements of service as the distinction actually lies between specialist and generalist. As RA is relatively uncommon and GPs have limited knowledge about the disease, much of its care needs to be managed by specialists. However, there needs to be better links between specialists and the community they serve and good working relationships between GPs and specialists and this might be better served by basing specialist services within the community. Better professional relationships could also be established by inviting community services into specialist centres to meet specialists and to organise teaching sessions. These ties would need to be continually maintained and would require commitment from both sides as it is unlikely that monetary resources would be available through the NHS although other sources could be sought. However, RA patients often need

direct access to X-rays and other specialist opinions. Exact solutions would have to be determined at a local level depending on issues such as travel for patients and local community facilities. This is a controversial matter that cannot be readily resolved.

CHAPTER 4. OVERLOOKED AREAS: FATIGUE

4.1. INTRODUCTION

Fatigue is common in rheumatoid arthritis (RA) and its absence characterises disease remission [Pinals et al. 1981]. Qualitative studies have highlighted the importance people with RA attribute to fatigue [Carr et al. 2003; Ahlman et al. 2005]. Between 40-80% of RA patients attending specialist clinics have clinically relevant fatigue, which is a feature of active disease. [Belza 1995; Belza et al. 1993; Pinals et al. 1981; Wolfe et al. 1996] By contrast few cases (under 5%) are in remission [Balsa et al. 2004], in which there is no fatigue. These observations suggest disease activity is one underlying factor, in the pathogenesis of fatigue in RA. Surprisingly the ways in which disease activity influence RA fatigue has not been investigated to any extent.

In early RA, fatigue has been shown to be a dominant factor in determining quality of life and psychosocial aspects of daily living. The exact cause of fatigue in RA has not been established but several studies have shown that fatigue correlates most strongly with pain and depression [Jump et al. 2004, Huyser et al. 1998]. Wolfe coined the term "fibromyalgic RA" to describe the sub-set of patients with high levels of fatigue, pain and depression [Wolfe et al. 2004]. Previous studies have also shown that high fatigue scores are associated with greater levels of disability [van Hoogmoed et al. 2010]. This finding might be explained by fatigue being a marker of disease activity. Alternative explanations for the relationship of fatigue to disability include the interaction of fatigue with psychological symptoms or perhaps a more direct link to disability.

The key aim of this study is to define the relative contribution of RA disease activity to fatigue in comparison to factors such as pain and depression in established RA. These inter-relationships were examined in two cross-sectional studies using different instruments to assess fatigue. They also evaluated the comparative effects of DMARDs and anti-TNF on RA fatigue in prospective observational cohorts in both early and established RA.

A further study examined the relationship between fatigue and disability. Reducing disability is a key therapeutic aim in RA. The focus on improving disability by reducing synovial inflammation and joint damage has overshadowed treating other

potential drivers of disability. Fatigue exemplifies another treatable disability driver. RA patients find fatigue a troubling symptom and there is a growing consensus it should be a core RA outcome measure [Kirwan et al. 2007].

Several measurement tools evaluate RA fatigue. The simplest is the unidimensional fatigue VAS; this is easy to score but only assesses overall severity. Multidimensional tools might be preferable as fatigue is likely to be multi-factorial. One multidimensional measure, the functional assessment of chronic illness therapy fatigue scale (FACIT-F), has been employed in many trials in RA [Cella et al. 2003]. Another measure, the multidimensional assessment of fatigue (MAF) questionnaire, was specifically designed for RA fatigue [Belza 1995]. A third measure, the Multidimensional Fatigue Symptom Inventory (MFSI), is a comprehensive tool [Stein et al. 1998].

High fatigue scores are known to be associated with greater levels of disability [Pollard et al. 2006]. This relationship could be explained if fatigue is a marker of disease activity, or if it is associated with psychological symptoms that are driving disability or even if there is a direct link with disability. The associations between fatigue and RA disability were explored focusing on the different ways of measuring fatigue using either a visual analogue scale or multidimensional fatigue tools (MAF, MFSI and FACIT-F).

Currently there is no agreed best measure of fatigue in RA. Therefore a further analysis of this second study aimed to determine whether it is best to measure fatigue in RA using a unidimensional or multidimensional tool. It also explored what the current fatigue tools are actually measuring by using exploratory factor analysis and a rotated factor matrix, which would allow us to determine the most useful questions to capture fatigue in RA.

4.2. OUTLINE OF PATIENTS AND METHODS

4.2.1. Patients

4.2.1.1. Clinical Association Studies

The RA patients met the 1987 criteria of the American College of Rheumatology, and were attending outpatient clinics in south east London. There were two patient groups. The initial clinical association study assessed fatigue using a visual analogue scale (VAS); the second clinical association study (alternative measure study) also used the vitality scale of the SF-36 (Appendix 9) as an alternative measure of fatigue. Demographic details of the patients are summarised in Table 4.1.

Table 4:1 Patients in Clinical Association Studies

Variable	Initial Study (<i>n</i> =238)	Alternative Measure Study (<i>n</i> =274)
Female	189 (79%)	245 (76%)
Male	49 (21%)	76 (24%)
Age mean (range)	60 (26-85)	64 (24-91)
Disease duration mean (range)	11 (0-37)	12 (1-52)
Nodular Disease	49 (20.59%)	
Rheumatoid factor	199 (83.61%)	
Erosive Disease	155 (65.13%)	

4.2.2. Treatment Effects Studies

4.2.2.1. Early RA

Data collected from patients enrolled in the early rheumatoid arthritis network (ERAN) was used for the early rheumatoid arthritis study. ERAN is a national network of rheumatologists following outcomes in patients with RA for less than two years at enrolment. There are 19 centres across the UK and Ireland and standardised information is collected on case report forms at first presentation to secondary care, then again at 3 to 6 months, at 1 year and annually thereafter. The choice and intensity of drug treatment is left to the discretion of the individual centres.

4.2.2.2. Established RA

Data were collected from 54 patients receiving DMARDS and 30 patients receiving anti-TNF therapy in one rheumatology outpatient department in south east London.

These patients met the 1987 criteria for RA. Data were collected prior to treatment and after 6 months of DMARD therapy and after 3 months of anti-TNF therapy. Patients who stopped treatment for any reason were excluded.

4.2.2.3. Fatigue Measurements Study

For the fatigue measurements study, data were collected from 105 patients with RA as defined by the 1987 ACR criteria, who were consecutive attendees in a routine outpatient clinic at King's College Hospital. The sample comprised 80 females and 25 males. Their mean age was 60 years (range 24-88); mean disease duration 13 years (range 0.1-54) and 70% were rheumatoid factor positive. 20 patients were receiving biologics and 78 patients receiving single or combination disease modifying drugs. Their mean DAS28 was 4.53 (SD 1.44) and HAQ 1.49 (SD 0.8). At the time of assessment, the majority of patients (93 of 105, 89%) were taking DMARDs. Informed consent was obtained from each participant and the study was fully approved by the Research Ethics committee.

4.2.3. Assessments

4.2.3.1. Clinical Association Studies

Fatigue was measured using a 100mm VAS and the vitality subscale of the SF-36 questionnaire. Demographic data (age, sex and disease duration) was collected as well as information on treatment (current DMARDs and anti-TNF). Pain (100mm VAS), disease activity score (DAS) for 28 joint counts and its constituent components (28 tender joint counts, 28 swollen joint counts, patient-global assessment and ESR), early morning stiffness (EMS) in minutes, modified health assessment questionnaire (HAQ) score (Appendix 10) and physician global assessment score was recorded for each patient. Patients in the initial study were also assessed for the presence of erosive disease, nodules, rheumatoid factor, haemoglobin, creatinine, all concomitant medications and illnesses.

4.2.4. Treatment Effects Studies

4.2.4.1. Early RA

All ERAN patients completed baseline data at first presentation which includes demographic data including age, sex, ethnicity, concomitant diseases and any extra articular RA disease. At each visit disease activity measures including 28 tender and swollen joint counts, patient global assessment (visual analogue scale 0-100mm), physician global assessment and blood tests including ESR are undertaken, which also allows the DAS28 to be calculated for each patient. Patients are also asked to complete the HAQ and the short form 36 (SF-36) which is a generic health status measure at each visit.

4.2.4.2. Established RA

Demographic data including age, sex and disease duration were collected as was information on treatment comprising current DMARD therapy and anti-TNF. Pain (100mm visual analogue scale), disease activity score (DAS) for 28 joint counts and its constituent components, comprising 28 tender joint counts, 28 swollen joint counts, patient-global assessment (100mm visual analogue scale), ESR, early morning stiffness (EMS) in minutes, modified health assessment questionnaire (HAQ) score and physician global assessment score (100mm visual analogue scale) were recorded in all cases.

4.2.4.3. Fatigue Measurements Study

Fatigue was assessed using four measures: A double anchored 100mm visual analogue scale (VAS) and three fatigue questionnaires; the FACIT-F (Appendix 11), the MAF (Appendix 12) and the multidimensional fatigue symptom inventory (MFSI-Appendix 13)

All questionnaires were self administered. The FACIT-F is a 13 item questionnaire and scores range from 0-52, it is an inverse scale, the higher the score the less the fatigue. The FACIT-F has four subscales; General fatigue, physical fatigue, mental fatigue and vigour. The MAF contains 16 items and scores range from 0 (no fatigue) to 50 (severe fatigue). The MAF has four subscales; Severity, distress, degree of interference of daily living and timing. The MFSI includes 30 items and scores range

from -24 to 96. The MFSI has five subscales; General fatigue, emotional fatigue, mental fatigue, vigour and physical fatigue.

Anxiety and depression were assessed using the HADS (Appendix 14). This is a self completed questionnaire which has 14 items; seven items measure anxiety and 7 items measure depression. [Zigmond et al. 1983] Anxiety and depression are measured separately with a range of scores between 0 and 21 for each subscale. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over indicating clinical 'caseness'.

Demographic data (age and disease duration), physician global assessment, pain VAS, early morning stiffness and the disease activity score (DAS) for 28 joints and its constituents (tender joint count, swollen joint count, erythrocyte sedimentation rate (ESR) and patient global assessment) were recorded in all cases.

4.2.5. Analyses

4.2.5.1. Clinical Association Studies

Data analysis was done using the Statistical Package for the Social Sciences (SPSS for Windows 11). Fatigue was analysed in two ways. On a first approach, taking fatigue as a continuous variable, simple linear regressions were used to study the individual effects of continuous variables like age, pain, physical assessment, DAS, etc. The effects of binary variables were assessed with two sample t-tests. Bivariate correlations were also calculated for each variable with fatigue.

To determine the key factors that contribute to fatigue in rheumatoid arthritis, these univariate analyses were followed by a multiple linear regression model fitted to all the variables in a stepwise manner, paying special attention to multi-collinearities, interactions and potential mediating relationships.

4.2.6. Treatment Effects Studies

4.2.6.1. Early RA

Data analysis was done using the Statistical Package for the Social Sciences (SPSS for Windows 11). Simple descriptive analyses of baseline data were calculated.

Means for all 8 domains of the SF-36 were assessed. To investigate changes over time paired results at baseline and at 12 months were calculated and bivariate correlations and linear regression analyses were undertaken between different domains. Missing data were imputed using the standard method recommended for SF-36; whereby missing values were replaced by scale means where valid responses were available for at least half of the scale items.

4.2.6.2. Established RA

Data analysis was done using the Statistical Package for the Social Sciences (SPSS for Windows 11). To assess the effects of treatment two sample independent t-tests and bivariate Spearman's correlations were used.

4.2.6.3. Fatigue Measurement Study

Simple descriptive analyses (including means and standard deviations) were applied to all the data. Bivariate Spearman's correlations were carried out for each variable against HAQ and each measure of fatigue. Simple linear regression was undertaken; any variable which did not reach significance at this level was not included in any further analysis. Simple regression was followed by stepwise backward multiple regression using HAQ as the dependent variable. In the multiple regression model the DAS28 was used as the measure of disease activity, therefore, tender joint count, swollen joint count, ESR and patient global assessment were not used as the DAS28 is a composite measure of these variables. A multiple regression model for each measure of fatigue was undertaken. Collinearity analysis was carried out for each final model.

To explore the different dimensions captured in each fatigue questionnaire and also assess their relationship with anxiety and depression, simple descriptive analyses were applied to the data, as well as Spearman's correlations. In this study, correlations of $r \geq 0.6$ are reported as strong correlations, $r \geq 0.4$ and < 0.6 as moderate correlations and $r < 0.4$ as weak correlations. Cronbach's alpha was used to test the internal validity of the items in the fatigue questionnaires. Following this an exploratory factor analysis of the fatigue questionnaires was undertaken. Factor analysis can reduce complex interrelationships to a relatively simple linear

expression. A rotated factor matrix was performed with all the questions from each questionnaire as well as the fatigue VAS and the HADS scores. Unrotated factors define the most general patterns of relationship in the data and a rotated factor matrix can delineate the distinct clusters of relationships.

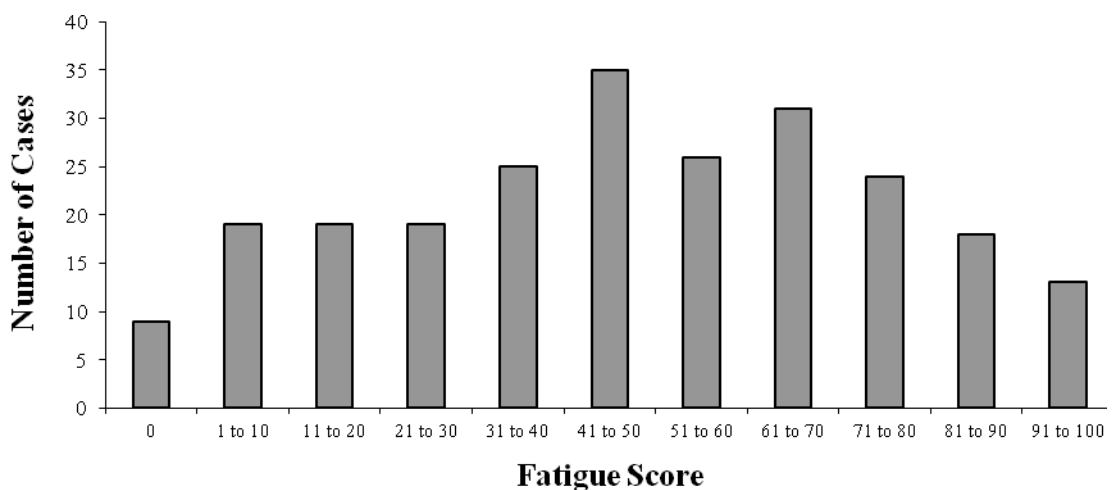
4.3. RESULTS

4.3.1. Fatigue and Its Clinical Associations

4.3.1.1. Frequency and Distribution of Fatigue

RA patients had high fatigue levels; 80% of patients had clinically relevant fatigue (VAS scores ≥ 20 mm) and over 50% had high fatigue scores (VAS scores ≥ 50 mm). The distribution of fatigue scores in this population is shown in Figure 4.1. Fatigue was also assessed by the SF-36 energy and vitality score (range 0-100). The lower the score the more severe the fatigue. The mean SF-36 energy and vitality score in the cohort was 51; which is substantially less than normal UK populations who have reported mean scores of 61-65.

Figure 4:1 Fatigue Scores in Initial Study



4.3.1.2. Correlations with Fatigue

The initial clinical association study showed VAS fatigue scores were significantly correlated with disease activity measures including DAS and VAS pain and also HAQ and early morning stiffness (Table 4.2). In addition there were significant associations with some co morbidities (number of concomitant diseases, depression

(fatigue score 68.6 vs. 47.6, $p=0.002$) and a previous diagnosis of fibromyalgia (fatigue score 72.1 vs. 47.7, $p=0.001$) and some prescribed drugs (methotrexate, tramadol and paracetamol). Fatigue was not associated with other DMARDs (sulphasalazine, hydroxychloroquine, leflunomide, gold, azathioprine, cyclosporin, d-penicillamine), anti-TNF therapy (etanercept, adalimumab, infliximab) and steroids (Table 4.3). It was also unrelated to age, disease duration, sex, rheumatoid factor, rheumatoid nodules, anaemia, diabetes mellitus, and renal, respiratory or ischaemic heart disease.

The second clinical association study (alternative measure study) showed similar significant correlations between VAS fatigue scores and both DAS and VAS pain scores. The SF-36 energy and vitality scores correlated (Spearman's rank correlation) strongly with fatigue VAS scores ($r=0.58$, $p<0.001$). Correlations with measures of disease activity were similar whether fatigue was measured using the VAS or the SF-36 energy and vitality score; SF-36 energy and vitality score (DAS $r=0.41$, $p<0.001$; HAQ $r=0.46$, $p<0.001$), VAS fatigue (DAS $r=0.47$, $p<0.001$; HAQ $r=0.46$, $p<0.001$). SF-36 mental health scores also showed a significant relationship with SF-36 energy and vitality score ($r=0.6$, $p<0.001$) as well as VAS fatigue ($r=0.46$, $p<0.001$).

4.3.1.3. Multiple Regression

Multiple linear regression in the initial clinical association study showed five variables explained 53% of variation in VAS fatigue scores (Table 4.4). Pain had the strongest association, then HAQ and depression. Methotrexate and erosive disease had negative associations, indicating patients receiving methotrexate had less fatigue and those without erosions had more fatigue.

Multiple linear regression in the second study showed three variables explained 53% of the variation in VAS fatigue scores (Table 4.4). Pain had the strongest positive association, followed by SF-36 mental health score (in an inverse scale a negative association indicates a positive relationship) and patient global assessment. Finally an ordinal regression model of the relationships of SF-36 energy and vitality scores showed three variables had significant associations: HAQ and pain had the strongest association followed by SF-mental health scores (Table 4.4).

**Table 4:2 Linear Regression Analysis of Fatigue VAS (a)
Continuous In Initial Study**

Variable	Coefficient	Significance
Age	-0.13	P=0.31
Disease Duration	-0.17	P=0.54
Early Morning Stiffness	0.08	P<0.001
Patient Global Assessment	0.64	P<0.001
Pain	0.66	P<0.001
Health Assessment Questionnaire	17.5	P<0.001
Tender Joint Count	1.8	P<0.001
Swollen Joint Count	1.7	P<0.001
Physician Global Assessment	0.43	P<0.001
ESR	0.18	P<0.01
DAS28	7.6	P<0.001
Haemoglobin	-0.79	P=0.49
Creatinine	-0.09	P=0.21
Number Concomitant Diseases	1.9	P<0.01

**Table 4:3 Regression Analysis of Fatigue VAS (b)
With Binary Variables**

Variable	Coefficient	Significance
Sex (male)	-5.3	p=0.22
Rheumatoid Factor	-3.8	p=0.41
Erosive Disease	-6.5	p=0.08
Nodules	-2.8	p=0.52
Methotrexate	-12.2	p<0.0001
Adalimumab	4.2	p=0.69
Etanercept	2.5	p=0.73
Infliximab	-9.7	p=0.43
Corticosteroids	3.5	p=0.59
Fibromyalgia	24.4	p<0.001
Diabetes	7.6	p=0.27
Depression	20.9	p=0.002
Hypothyroidism	4.6	p=0.54
Respiratory Disease	1.5	p=0.79
Ischaemic Heart Disease	11.4	p=0.08

Table 4:4 Factors Contributing To Fatigue
Fatigue Assessed Using VAS And SF-36 Vitality Scale. Analysis by Multiple Linear Regression

Initial Clinical Association Study (n=238)						Alternative Measure Clinical Association Study (n=274)					
Variable	Coefficient	95% Confidence Interval		P Value		Variable	Coefficient	95% Confidence Interval		P Value	
		Lower	Upper					Lower	Upper		
Fatigue (VAS) * Adjusted R ² = 0.53	Pain (VAS)	0.50	0.39	0.61	0.0001	Fatigue (VAS) ‡ Adjusted R ² = 0.53	Pain (VAS)	0.44	0.28	0.60	0.0001
	Modified HAQ	7.17	3.25	11.09	0.0001	Mental Health Score	-0.39	-0.51	-0.27	0.0001	
	Depression	10.73	1.18	20.29	0.03		Patient Global Assessment	0.16	0.02	0.31	0.03
	Methotrexate	-8.08	-13.00	-3.17	0.001	Energy and Vitality (SF-36) § Odds Ratio	Modified HAQ	1.95	1.35	2.81	0.0001
	Erosive Disease	-7.47	-12.62	-2.32	0.01		Pain (VAS)	1.02	1.01	1.03	0.0001
							Mental Health Score	0.95	0.94	0.97	0.0001

* Excluded variables: DAS 28, TJC, SJC, physician global assessment, patient global assessment, ESR, EMS, age, disease duration, sex, seropositivity, rheumatoid nodules, Hb, Cr, diabetes mellitus, hypothyroidism, respiratory disease, ischaemic heart disease, number of concomitant diseases, fibromyalgia, tramadol, paracetamol, sulphasalazine, hydroxychloroquine, leflunomide, gold, azathioprine, cyclosporin, d-penicillamine, anti-TNF therapy, corticosteroids.

‡ Excluded variables: DAS 28, TJC, SJC, physician global assessment, HAQ, EMS, CRP, ESR, age, sex, disease duration.

§ Excluded variables: DAS 28, TJC, SJC, physician global assessment, patient global assessment, EMS, CRP, ESR, age, sex, disease duration.

4.3.2. Effects of Treatment on Fatigue in RA

4.3.2.1. Early RA

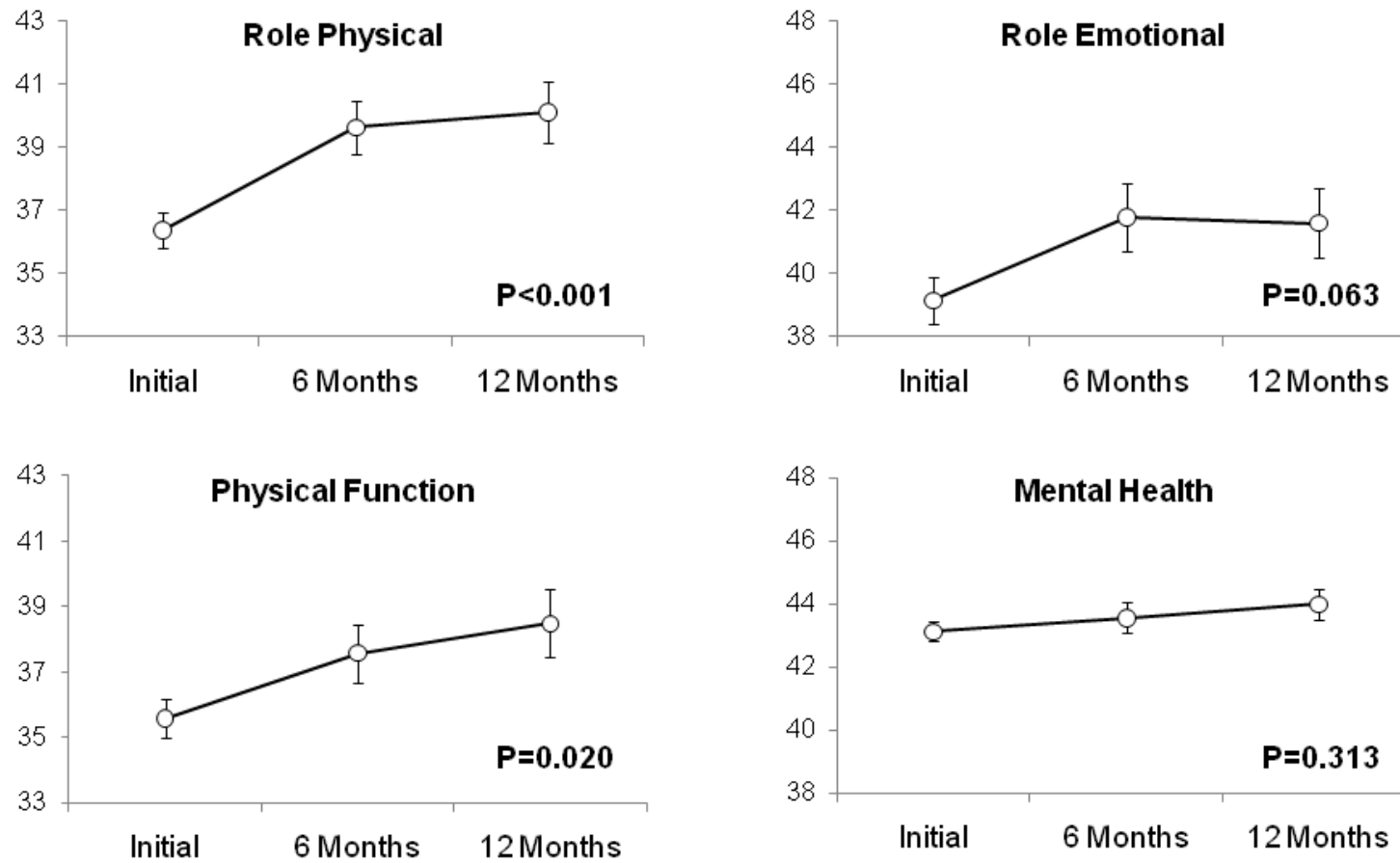
The sample was comprised of 265 females and 130 males. The mean age was 55 years (range 18-88). The ethnic grouping of patients recruited into the study represented Caucasian, 96% and others 4%. At initiation into ERAN, 378 patients were on single or combination DMARD therapy, which comprised 17 patients on hydroxychloroquine, 148 on sulfasalazine, 173 on methotrexate, 11 on other monotherapy and 29 on combination DMARDs. At baseline the mean DAS28 was 4.78 (SD 1.55), ESR 32(SD 25), tender joint count 8 (SD 7), swollen joint count 6 (SD 6), CRP 25 (SD 33) and HAQ 1.1 (SD 0.8).

The SF-36 showed substantial reductions in quality of life in patients with early RA, compared to reported general populations [Garratt et al. 2003]. There was major impact on physical function (mean 35.6, SE 0.6), general health (mean 44.3, SE 0.3), social function (mean 35.7, SE 0.2), mental health as well as vitality/fatigue (mean 48.4, SE 0.3). (Table 4.5)

After twelve months of treatment there were improvements in physical function (mean increase 2.5 (SD 11.8); $p=0.01$) and in role physical (mean increase 2.2 (SD 12.1); $p=0.03$). However, there were no significant changes in vitality (fatigue), social function and mental health domains. (Figure 4.2)

Table 4:5 SF-36 in Early RA Patients

	Mean Values			
SF-36 Measures	Early RA Patients			General Population
	<i>Baseline Visit</i>	<i>6 Months</i>	<i>12 Months</i>	<i>[Garratt et al, 2003]</i>
Physical Functioning	35.6	37.6	38.5	79.2
Role Physical	36.4	39.6	40.1	76.5
Bodily Pain	41.1	37.9	38.0	76.9
General Health	44.3	43.6	44.0	68.7
Vitality	48.4	48.8	47.6	61.2
Social Functioning	35.7	35.8	35.7	78.6
Role Emotional	39.1	41.8	41.6	75.0
Mental Health	43.1	43.6	44.0	73.7

Figure 4:2 Changes with Treatment in SF-36 in Early RA.

4.3.2.2. Established RA

DMARDs: The sample comprised 54 patients with a mean age of 62 (range 33-82), mean disease duration of 10 years (range 1-42), mean fatigue VAS 56 (SD 27.2), mean pain VAS 61 (SD 25.2) and mean DAS28 5.7 (range 2.7-8.5)

Over 6 months VAS fatigue scores fell from a mean of 56 to 49 ($p=0.176$). Pre-treatment 34 (63%) of patients had high levels of fatigue (VAS scores ≥ 50 mm); post treatment this fell to 26 (48%). The falls in VAS fatigue scores correlated with improvements in pain and DAS-28 ($r=0.63$, $p<0.001$ and $r=0.69$, $p<0.001$ respectively). The effect sizes of DMARD therapy on DAS, pain and fatigue were 79%, 66% and 42% respectively.

Anti-TNF: The sample comprised 30 patients with a mean age of 53 (range 22-81), mean disease duration of 15 years (range 1-33), mean fatigue VAS 67 (SD 21.9), mean pain VAS 65 (SD 21.9) and mean DAS28 6.1 (range 3.7-7.8)

Prior to treatment, the VAS fatigue score of anti-TNF treated patients were statistically significantly higher than DMARD treated patients (67 vs. 56, $p=0.04$) although post-treatment it was similar in both groups (50 vs. 49). Over 3 months there was a mean fall in VAS fatigue score of 67 to 50 ($p=0.009$). Pre-treatment 26 (87%) of patients had high levels of fatigue (VAS scores ≥ 50 mm); post treatment this fell to 15 (50%). The falls in VAS fatigue scores correlated with improvements in pain and DAS-28 ($r=0.65$, $p<0.001$ and $r=0.43$, $p=0.019$ respectively). The effect sizes of anti-TNF therapy on DAS, pain and fatigue were 128%, 80% and 73% respectively.

4.3.3. Fatigue Measurement Study

4.3.3.1. Fatigue and Disability

Median scores for HAQ were 1.6 and for the fatigue measures were between 25 and 54 (Table 4.6). Allowing for scaling differences by calculating median percent maximum scores showed they all assessed disability and fatigue at a similar level (HAQ 54%, MAF 56%, MRSI 58%, and FACIT 54%).

The different fatigue scores had varying relationships to HAQ when this was divided into 6 categories (Figure 4.3). VAS scores showed a straightforward linear relationship; it was equally sensitive at high and low levels of disability. The other three scores showed “ceiling” effects; so that once disability scores were more than 1.50 (50% maximum score) there was very little change in the fatigue scores. Suggesting that fatigue scores increase with disability scores but once disability scores reach a certain level fatigue scores have already reached a maximum and can no longer increase with further increases in disability scores. The inverse nature of the FACIT score did not impact on this relationship.

Simple linear regression showed significant associations between HAQ and all variables (disease duration, pain VAS, tender joint count, swollen joint count, ESR, patient and physician global assessment, DAS28, anxiety, depression and all fatigue measures) except age ($p=0.18$) and early morning stiffness ($p=0.13$); these two variables were therefore not included in the final multivariate analysis.

Bivariate correlations showed significant correlations between HAQ and all variables except for age ($r=0.13$) (Table 4.6). HAQ showed moderate correlations with each fatigue measure (0.38 vs. Fatigue VAS, 0.32 vs. MAF, 0.38 vs. MFSI, -0.46 vs. FACIT-F)

The various fatigue assessments were all inter-related. VAS fatigue scores showed moderate correlations with the other fatigue measures (Spearman's $R=0.52$ vs. MAF, 0.43 vs. MFSI and -0.54 vs. FACIT-F. Other fatigue scores showed moderate to high correlations with each other (0.77 MAF vs. MFSI; -0.77 MFSI vs. FACIT-F; -0.83 MFSI vs. FACIT-F).

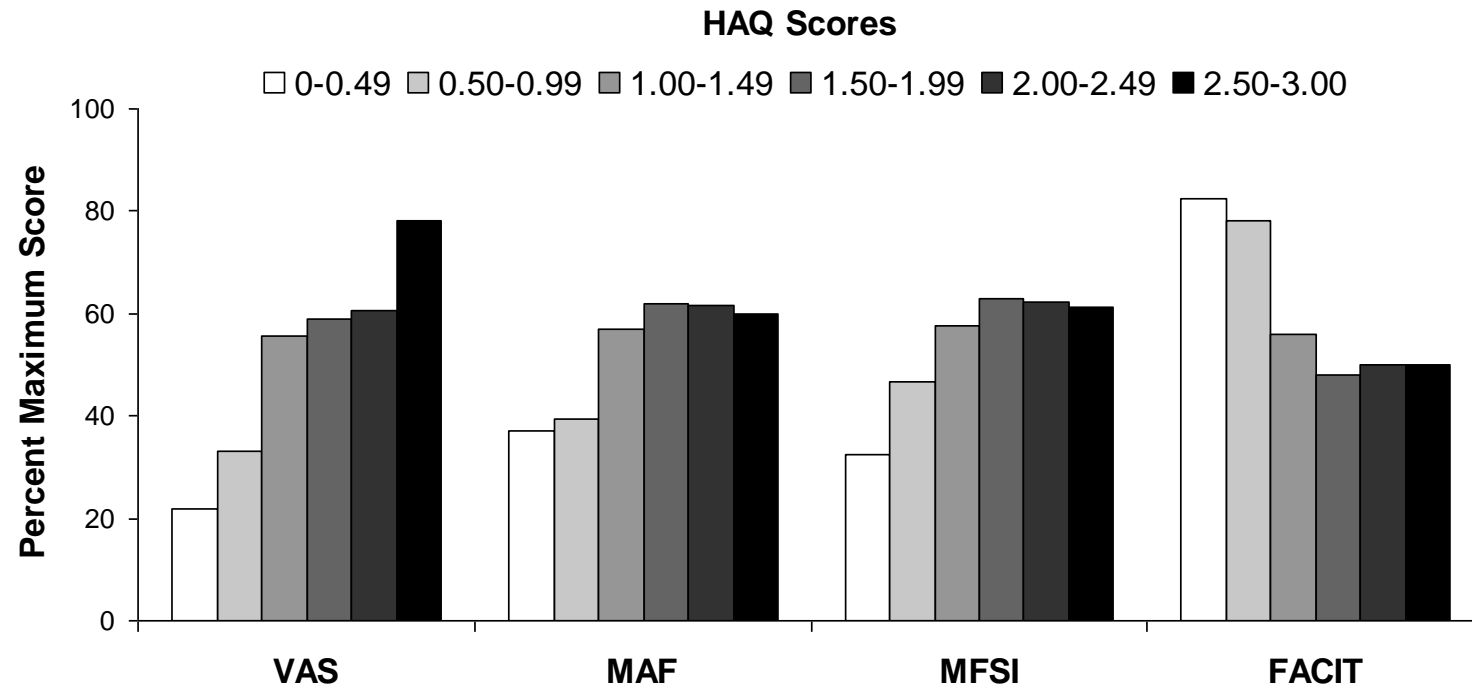
The fatigue measures all showed moderate bivariate correlations with DAS28 (0.31-0.54). The fatigue VAS had strong correlations with pain and was the only fatigue measure to correlate with the ESR (Table 4.6). MAF, MFSI and FACIT-F showed stronger correlations with HADS anxiety and depression scores. None of the fatigue measures showed significant correlations with age, disease duration, swollen joint counts or physician global assessment.

Table 4:6 HAQ and Fatigue Scores
Medians (Interquartile Ranges) and Spearman's Correlations are shown.

	Range	Median (IQR)	Bivariate Correlation (Spearman's)									
			<i>DAS28</i>	<i>Pain</i>	<i>TJC</i>	<i>SJC</i>	<i>ESR</i>	<i>PGA</i>	<i>EMS</i>	<i>Disease Duration</i>	<i>HADS Anxiety</i>	<i>HADS Depression</i>
HAQ	0 – 2.75	1.62 (1.00, 2.12)	0.57	0.43	0.46	0.21	0.35	0.46	0.29	0.28	0.33	0.46
Fatigue VAS	0 – 100	54 (35, 78)	0.54	0.59	0.45	0.13	0.24	0.51	0.25	-0.13	0.41	0.46
MAF	0 – 50	28 (21, 35)	0.31	0.34	0.33	0.01	0.03	0.35	0.30	-0.15	0.58	0.67
MFSI	-24 – 96	25 (13, 43)	0.34	0.28	0.41	-0.08	0.01	0.35	0.29	-0.11	0.76	0.69
FACIT-F	0 – 52	27 (19, 38)	-0.40	-0.38	-0.39	-0.01	-0.10	-0.43	-0.29	0.13	-0.58	-0.70

TJC – Tender Joint Count, SJC – Swollen Joint Count, PGA – Patient Global Assessment, EMS – Early Morning Stiffness

Figure 4:3 Fatigue Scores and HAQ Categories
Median Percent Maximum Fatigue Scores Are Shown For Each Measure. HAQ Is Divided Into 6 Categories



Fatigue scores were normally distributed and mean (range) fatigue scores comprised fatigue VAS 55 (0-100), MAF 27 (0-50), MFSI 26 (-14-75) and FACIT-F 28 (5-52). All fatigue scores correlated with HAQ: fatigue VAS ($r=0.38$, $p<0.001$), MAF ($r=0.32$, $p<0.001$), MFSI ($r=0.38$, $p<0.001$) and FACIT-F ($r=-0.46$, $p<0.001$). Backward stepwise regression analyses with HAQ as the dependent variable (Table 4.7) showed MAF, MFSI and FACIT-F were all independent predictors of HAQ, but fatigue VAS was not. DAS28 and disease duration contributed to the variation in HAQ in all four regression models. Up to 50% of the variation in HAQ was explained by changes in DAS28, FACIT-F and disease duration (model 4).

Table 4:7 Linear Regression with HAQ as Dependent Variable

Fatigue Measure	Variable	Coefficient B	95% confidence Interval		P Value
			<i>Lower</i>	<i>Upper</i>	
Fatigue VAS	DAS28	0.26	0.21	0.30	<0.001
	Disease Duration	0.02	0.02	0.03	<0.001
	Anxiety	0.05	0.03	0.06	0.002
		R²=0.44			
MAF	DAS28	0.25	0.21	0.29	<0.001
	Disease Duration	0.02	0.02	0.03	<0.001
	MAF	0.02	0.01	0.03	0.001
		R²=0.45			
MFI	DAS28	0.24	0.19	0.28	<0.001
	Disease Duration	0.02	0.02	0.03	<0.001
	MFI	0.01	0.01	0.01	0.001
		R²=0.46			
FACIT-F	DAS28	0.21	0.17	0.26	<0.001
	FACIT-F	-0.02	-0.03	-0.02	<0.001
	Disease Duration	0.02	0.02	0.03	<0.001
		R²=0.50			

4.3.4. Fatigue Measurement Study

Simple descriptive statistics with means and standard deviations are shown in Table 4.8. The fatigue questionnaires showed strong correlations with each other using Spearman's correlation (MAF and MFSI $r=0.78$, $p<0.001$, MAF and FACIT-F $r=-0.76$, $p<0.001$, MFSI and FACIT-F $r=-0.80$, $p<0.001$). They also showed strong correlations with the HADS anxiety and depression scores. In contrast the fatigue VAS was most strongly correlated with the pain VAS ($r=0.59$, $p<0.001$). The fatigue questionnaires had weaker correlations with pain VAS (Table 4.9).

Table 4:8 Fatigue Questionnaires Descriptive Analysis

	Patient Number*	Mean (SD)
Pain VAS	105	49.8 (29.1)
Fatigue VAS	105	54.7 (27.5)
HAQ	98	1.5 (0.8)
HADS Anxiety	98	7.9 (4.3)
HADS Depression	98	6.1 (3.8)
MAF	98	26.8 (11.1)
MFSI	97	26.4 (21.3)
FACIT	97	28.4 (11.5)

*Questionnaires with missing data were excluded from the analysis.

Cronbach's alpha was calculated for internal validity for all items in the fatigue questionnaires. This showed an overall Cronbach's alpha of 0.82 (standardised 0.76), indicating good overall reliability.

Table 4:9 Spearman's Correlations with Different Fatigue Questionnaires

	Pain VAS	Fatigue VAS	HAQ	HADS Depression	HADS Anxiety	MAF	MFSI
Fatigue VAS	0.59 [†]	-	-	-		-	-
HAQ	0.43 [†]	0.38 [†]	-	-	-	-	-
HADS Depression	0.46 [†]	0.46 [†]	0.46 [†]	-	-	-	-
HADS Anxiety	0.34 [*]	0.41 [†]	0.33 [*]	0.67 [†]	-	-	-
MAF	0.34 [*]	0.50 [†]	0.32 [*]	0.67 [†]	0.88 [†]	-	-
MFSI	0.28 [*]	0.42 [†]	0.38 [†]	0.69 [†]	0.76 [†]	0.78 [†]	-
FACIT-F	-0.38 [†]	-0.54 [†]	-0.46 [†]	-0.70 [†]	-0.58 [†]	-0.76 [†]	-0.80 [†]

† p<0.001

* p<0.01

All questions from the fatigue multidimensional questionnaires were then entered into a factor analysis. Five dominant factors were identified that contributed to fatigue in RA. The five factors contributing to fatigue were: (1) psychological factors (anxiety/depression); (2) cognition; (3) fatigue severity; (4) physical interference; (5) social interference. The fatigue VAS did not load significantly into any category; its highest loading was severity (0.43). Of the 45 questions entered into the factor matrix, 12 questions loaded significantly (≥ 0.50) into factor 1 (psychological factors), 10 questions loaded significantly into factor 2 (cognition), with 4 questions loading into factor 3 (fatigue severity), 3 questions loading into factor 4 (physical interference) and 4 questions loading into factor 5 (social interference). There were 12 questions which did not load significantly into any factor. (Table 4.10)

Each questionnaire was examined separately to determine which were the major factors being measured by the individual multidimensional tools. For the FACIT-F the major contributing factor was cognition with 7 questions loading into that factor, there was a small contribution from severity with 1 question loading into that factor. For the MAF the questions loaded into 3 factors, the predominance was for measuring the impact of fatigue on daily living with 4 questions loading into factor 4 (physical interference) and 4 questions loading into factor 5 (social interference), there was also a contribution from severity of fatigue with 3 questions loading into factor 3. For the MFSI questionnaire most questions loaded into 2 factors; the predominant factor was psychological factors with 11 questions loading into factor 1 (psychological factors) and 3 questions loading into factor 2 (cognition). (Table 4.11)

In order to identify the most appropriate questions, only items which loaded strongly into each dimension (loading > 0.6) were included; this reduced the number of questions to 25. To further reduce this both clinical interpretation and statistics were employed to exclude any very similar questions; keeping the question with the highest loading. For example: I feel nervous and I feel tense were felt to be asking the same question. The loading into the factor analysis rotated factor analysis was 0.889 for I feel nervous and 0.672 for I feel tense; therefore, I feel tense was excluded from the final model. Consideration was also made to ensure that each dimension was represented. This left us with 18 questions, which are shown in Table 4.12.

Table 4:10 Factor Analysis Using Rotated Matrix

	1 Psychological Factors	2 Cognition	3 Severity	4 Physical Interference	5 Social Interference
Fatigue-VAS	0.063	0.281	0.432	0.275	-0.091
HADS anxiety score	0.715	0.326	0.119	0.228	0.053
HADS depression score	0.335	0.538	0.232	0.330	0.126
Individual Questions from Questionnaires					
Feel fatigued	-0.134	-0.406	-0.682	-0.089	-0.046
Feel listless (“washed out”)	-0.233	-0.609	-0.303	-0.086	-0.261
Feel tired	-0.188	-0.592	-0.432	-0.024	-0.261
Feel weak all over	-0.182	-0.597	-0.350	-0.301	-0.132
Have trouble starting things because I am tired	-0.337	-0.706	-0.122	-0.154	-0.222
Have trouble finishing things because I am tired	-0.375	-0.647	-0.229	-0.034	-0.234
Able to do my usual activities	0.010	-0.375	-0.177	-0.277	0.057
Need to sleep during the day	-0.307	-0.401	-0.080	-0.312	0.000
Am too tired to eat	-0.349	-0.386	-0.215	-0.090	0.016
Have to limit social activity because tired	-0.273	-0.706	-0.263	-0.287	-0.235
Have energy	-0.104	-0.274	-0.396	-0.061	-0.096

	1 Psychological Factors	2 Cognition	3 Severity	4 Physical Interference	5 Social Interference
Frustrated by being too tired to do the things	-0.370	-0.593	-0.172	-0.067	-0.260
To what degree have you experienced fatigue?	0.169	0.287	0.869	0.205	0.115
Severity of fatigue	0.185	0.193	0.848	0.289	0.150
How often fatigued last week?	0.217	0.221	0.638	0.136	0.250
Degree fatigue caused you distress	0.586	0.301	0.372	0.397	0.053
Degree fatigue interfered with household chores	0.170	0.385	0.345	0.328	0.252
Degree fatigue interfered with cooking	0.252	0.331	0.274	0.591	0.214
Degree fatigue interfered with bathing/washing	0.251	0.277	0.192	0.823	0.124
Degree fatigue interfered with dressing	0.330	0.314	0.169	0.791	0.136
Degree fatigue interfered with working	0.129	0.037	0.087	0.331	0.365
Degree fatigue interfered with socialising	0.099	0.40	0.268	0.366	0.40
Degree fatigue interfered with sex	0.062	-0.030	0.111	0.086	0.717
Degree fatigue interfered with leisure	0.032	0.023	0.004	-0.039	0.823
Degree fatigue interfered with shopping/errands	0.019	0.154	-0.001	0.034	0.601
Degree fatigue interfered with walking	-0.031	0.219	0.131	-0.020	0.355
Degree fatigue interfered with exercise	-0.019	0.184	0.107	0.114	0.694
Trouble remembering things	0.481	0.105	-0.002	0.105	-0.204

	1 Psychological Factors	2 Cognition	3 Severity	4 Physical Interference	5 Social Interference
Confused	0.645	0.092	-0.016	0.147	-0.136
Trouble paying attention	0.656	0.026	0.175	0.142	0.137
Unable to concentrate	0.700	0.220	0.046	0.081	0.018
More mistakes than usual	0.526	0.214	0.111	0.190	-0.022
Forgetful.	0.625	0.103	0.007	-0.007	-0.178
Muscles ache	0.175	0.637	0.175	0.313	0.005
Legs feel weak	0.128	0.543	0.249	0.326	0.028
Head feels heavy	0.328	0.190	0.115	0.244	0.107
Arms feel weak	0.283	0.364	0.211	0.495	-0.103
Ache all over	0.292	0.452	0.274	0.395	-0.100
Body feels heavy all over	0.404	0.521	0.119	0.208	0.108
Feel upset	0.889	0.096	0.146	0.084	0.077
Feel nervous	0.864	0.164	0.073	0.074	0.092
Feel sad	0.723	0.239	0.163	0.121	0.215
Feel depressed	0.755	0.183	0.182	0.132	0.242
Feel tense	0.672	0.289	0.191	0.083	0.113
Distressed	0.762	0.103	0.144	0.125	0.196

Table 4:11 Dimensions In Fatigue Questionnaires

	Fatigue Dimensions - Number of Questions Represented				
	<i>1</i> <i>Psychological</i>	<i>2</i> <i>Cognition</i>	<i>3</i> <i>Severity</i>	<i>4</i> <i>Physical Interference</i>	<i>5</i> <i>Social Interference</i>
FACIT-F	0	7	1	0	0
MAF	0	0	3	4	4
MFSI	11	3	0	0	0

Table 4:12 Proposed Questions for Final Fatigue Questionnaire

Items	Factors				
	1	2	3	4	5
Psychological					
I am confused	0.645	0.092	-0.016	0.147	-0.136
I am unable to concentrate	0.700	0.22	0.046	0.081	0.018
I feel upset	0.889	0.096	0.146	0.084	0.077
I feel nervous	0.864	0.164	0.073	0.074	0.092
I am distressed	0.762	0.103	0.144	0.125	0.196
Cognition					
My muscles ache	0.175	0.637	0.175	0.313	0.005
I feel listless (“washed out”)	-0.233	-0.609	-0.303	-0.086	-0.261
I have trouble <u>starting</u> things because I am tired	-0.337	-0.706	-0.122	-0.154	-0.222
I have trouble <u>finishing</u> things because I am tired	-0.375	-0.647	-0.229	-0.034	-0.234
I have to limit my social activity because I am tired	-0.273	-0.706	-0.263	-0.287	-0.235
Severity					
To what degree have you experienced fatigue?	0.169	0.287	0.869	0.205	0.115
How severe is the fatigue which you have been experiencing?	0.185	0.193	0.848	0.289	0.150
Over the past week, how often have you been fatigued?	0.217	0.221	0.638	0.136	0.250
Physical Interference					
To what degree has fatigue interfered with your ability to bathe or wash?	0.251	0.277	0.192	0.823	0.124
To what degree has fatigue interfered with your ability to dress?	0.330	0.314	0.169	0.791	0.136
Social Interference					
To what degree has fatigue interfered with your ability to engage in leisure and recreational activities?	0.032	0.023	0.004	-0.039	0.823
To what degree has fatigue interfered with your ability to shop and do errands?	0.019	0.154	-0.001	0.034	0.601
To what degree has fatigue interfered with your ability to exercise, other than walking?	-0.019	0.184	0.107	0.114	0.694

The questions taken from the FACIT-F questionnaire will have negative values as this is an inverse scale, therefore the lower the score the worse your fatigue

4.4. DISCUSSION

4.4.1. Fatigue and Its Clinical Associations

Fatigue is a dominant symptom in RA. In keeping with previous reports [Huyser et al. 1998; Riemsma et al. 1998; Rupp et al. 2004; Tack 1990; Fifield et al. 1998; Wolfe et al. 2004; Suurmeijer et al. 2001; Fifield et al. 2001; Crosby 1991; Jump et al. 2004] the results of this study showed it is strongly associated with pain. Patients with active RA had high levels of fatigue, but multiple regression analyses show this relationship was less important than the association with pain. Patients diagnosed with either fibromyalgia and/or depression have higher levels of fatigue. These conditions co aggregate and after adjustment with multivariate analysis, depression is the only co-morbidity invariably associated with fatigue. Other co-morbidities including cardiovascular and respiratory diseases were not directly related. Several other factors are associated with fatigue scores; HAQ scores were positively associated, indicating patients with high fatigue levels are markedly disabled. Methotrexate use and erosive disease had negative relationships. This suggests that methotrexate use is associated with lower levels of fatigue, which may have two explanations; firstly patients who are treated with methotrexate have a better outcome, secondly that the non-methotrexate treated patients represent a different subset of RA patients. The association of non-erosive disease and higher fatigue scores may also represent a specific subset of RA patients in this population. Interestingly there were no association between fatigue and age or disease duration, indicating peripheral features like muscle mass, which decreases with age and disease duration are unimportant. One possible explanation for the lack of association between fatigue, disease duration and other peripheral features is that fatigue in RA may be central in origin.

If fatigue is to be used as an RA outcome measure, it is crucial to identify the best assessment instrument. VAS fatigue scores are simple and reproducible; however, multidimensional assessments may provide a more complete picture and improve understanding of the clinical relationships of fatigue. There were similar results using VAS scores and SF-36 energy and vitality scores and when Wolfe [Wolfe 2004] compared VAS scores with three multidimensional fatigue scales he also found that the VAS fatigue performed favourably compared to more detailed scales.

Nevertheless other validated and detailed instruments that measure RA fatigue, such as the Multidimensional Assessment of Fatigue (MAF) [Belza et al. 1993] and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [Cella et al. 2005], may prove more valuable especially for studies which assess the mechanism of fatigue rather than using it simply as another outcome measure.

In conclusion, high fatigue levels are common in RA and in this study are predominantly linked to pain and depression. In this cohort the association with disease activity appears to be secondary.

4.4.2. The Effect of Treatment on Fatigue in RA

RCTs provide some evidence that adalimumab [Weinblatt et al. 2003]; methotrexate and leflunomide [Strand et al. 2005] reduce fatigue. These falls in fatigue accompanied decreases in disease activity. The observational studies in established disease show that in routine practice fatigue decreases when active RA is treated with anti-TNF and to a lesser extent with DMARDs. These falls mirror decreases in DAS scores and pain. Although Wolfe and Michaud [Wolfe et al. 2004] found similar levels of fatigue in RA patients on anti-TNF therapy and those not receiving biologics, they did not measure fatigue levels prior to commencement of anti-TNF and their results are best explained by confounding by indication. Meaning that fatigue levels may have been higher initially in the patients who received anti-TNF but fatigue was only measured after they received treatment and fatigue levels were then similar to patients treated with DMARDs. It is then impossible to say whether anti-TNF had a greater effect on fatigue than DMARDs as fatigue may have been significantly higher in the patients who went on to receive anti-TNF compared to those who received DMARDs. Indeed the data from this study indicates that patients started on anti-TNF therapy had higher fatigue scores at baseline.

TNF receptors have been identified on neurons [Pollock et al. 2002] and chronic inflammation is associated with upregulation of these TNF receptors [Inglis et al. 2005]. TNF has also been implicated in pain pathways [Empl et al. 2001] and thus in conditions such as RA the increase in TNF levels may contribute to chronic

inflammatory pain. The improvement in pain and fatigue with anti-TNF therapy may be due to a direct central effect through interaction with sensory neurons.

The early RA study highlights the impact of early RA across most aspects of health. The SF-36 showed substantial overall reductions in quality of life, compared to normal populations [Garratt et al. 2003]. Although treatment over twelve months showed improvements in the physical domains of the SF-36 (physical function and role physical) there were no significant changes in vitality, social function and mental health domains. This would suggest that a broader range of treatment approaches would benefit early RA patients, focusing on mental as well as physical health. One reason for not demonstrating an improvement in fatigue with treatment in this group of patients may be in part related to the way in which fatigue was measured in these patients. There is no agreed best method of measuring fatigue in RA and there are disease specific questionnaires such as the MAF and generic measures such as the SF-36. Although there is some evidence of validation for measuring fatigue in RA with the SF-36 vitality scale, Hewlett et al [Hewlett et al. 2007] felt that the scale would benefit from further research, particularly concerning content validity for patients with RA and sensitivity to change. Further work using different measures of fatigue in RA are recommended to clarify this point.

4.4.3. Fatigue and Disability

RA disability is influenced by disease activity, joint damage, co morbidities, psychosocial factors and depression [Pollard et al. 2006; Esclante et al. 1999; Sokka et al. 2000; Wolfe 2000; Rupp et al. 2006; Gettings et al. 2010; Hazes et al. 2010]. Many of these factors have cultural contexts [Ravindran et al. 2008; Griffiths et al. 2000; Bruce et al. 2007]. The results from our study confirm that fatigue is another important contributor to disability in RA. The relationship between fatigue and disability depends on how fatigue is measured. It is only when multidimensional tools are used (MAF, MFSI and FACIT-F) that the effects of fatigue on disability become apparent. The multidimensional fatigue measurements incorporate psychological factors, and were strongly correlated with HADS depression and anxiety scores; however, multivariate analyses took these relationships into account and still showed the multidimensional fatigue questionnaires had stronger

associations with disability. The results suggest while fatigue seems to be strongly associated with psychological factors when measured by multidimensional tools it independently contributes to disability in RA, suggesting that it is measuring something more than just anxiety and depression.

The findings have several limitations. The patient sample was relatively small and came from one centre with an ethnically diverse population. The patients were receiving different treatments and were at different stages of their disease. Changes over time were not evaluated. Finally, it is not possible to determine causality from these results; they cannot differentiate fatigue being disabling from disabled patients being more fatigued. However, they show there is a complex interaction between fatigue, psychological factors and disability, and this interaction explains why multidimensional tools perform better than the unidimensional VAS in predicting disability.

Effective RA management involves reducing disease activity but also targeting factors like fatigue. The findings in this study suggest it is better to assess fatigue using multidimensional tools. The wide use and simplicity of the FACIT-F make it the current multidimensional instrument of choice.

4.4.4. Fatigue Questionnaires: What Is Actually Being Measured?

One of the difficulties of studying fatigue in RA is the lack of agreement over which is the best measure of fatigue in RA. Different studies often use different fatigue tools meaning that comparison between studies is difficult. There is also a lack of agreement by what is actually meant by fatigue and what it is actually measured with current questionnaires and the important dimensions that should be measured. [Nikolaus et al. 2012] The present study used a simple visual analogue scale for fatigue which has the advantage of being quick and easy to administer and score as well as three different fatigue questionnaires. The MAF was designed specifically for RA patients so has the advantage of being disease specific, the FACIT-F has been widely used and seems to be the fatigue questionnaire of choice in many drug trials. The MFSI is one of the more comprehensive tools.

There was strong correlation between all three questionnaires but less so with the fatigue VAS, this correlated most strongly with the pain VAS. The reason for the strong correlations between pain and fatigue VAS may in part be related to the way in which they are measured, as they are both measured using a visual analogue scale. When factor analysis was applied to the questions from all the questionnaires five factors or dimensions were identified. These were psychological distress/cognition, severity, physical and social interference. These five factors/dimensions are very similar to the dimensions described by the Bristol research group who have recently designed a new fatigue measure for RA (BRAFF-MDQ) [Nicklin et al. 2010]. Their dimensions included Living (questions on physical and social interference), cognition, emotion and physical (questions on physical interference and severity). Although five important dimensions were identified none of the established questionnaires in the study measured all five dimensions. Questionnaires were often heavily weighted to one domain over another. The FACIT-F was predominantly measuring cognition; MFSI was predominantly measuring psychological factors and the MAF was predominantly measuring the impact of fatigue (physical and social interference).

As five important factors/dimensions of fatigue have been identified in this study, as in the Bristol study [Nicklin et al. 2010], an ideal fatigue questionnaire for RA should include all five dimensions/factors. In this study using statistics and clinical judgement we identified 18 questions which covered all dimensions which could make an appropriate questionnaire. Interestingly, there is significant overlap in the questions suggested in this study and the questions in the BRAFF-MDQ with nine of the questions being identical or very similar. To determine the usefulness of the suggested items; the proposed questionnaire would need to be subject to test and retest as well as checks for internal consistency and validity. This requires further research.

When deciding which measure to use in future studies, of the currently widely used questionnaires the FACIT-F compares well to other questionnaires and is quick and easy to use. However, it has limitations as described above. The BRAFF-MDQ has yet to be widely used but may prove to be the preferred multidimensional fatigue tool.

CHAPTER 5. CLINICAL SUBTYPES: FIBROMYALGIC DISEASE

5.1. INTRODUCTION

5.1.1. Fibromyalgic Rheumatoid

Rheumatoid arthritis (RA) spans several distinct clinical phenotypes. One of these includes coexisting fibromyalgic features; this phenotype has been termed “fibromyalgic RA” [Scott et al. 2007]. Its importance has been highlighted by Wolfe and colleagues who described its characteristic high levels of pain, fatigue and disability [Wolfe et al. 1984; Wolfe et al. 2004]. It is estimated that approximately 10%-20% of RA patients have the subtype fibromyalgic RA.

The high pain and disability scores that are seen in fibromyalgic RA suggest that these patients will also have high scores using summative assessments such as the Disease Activity Score for twenty-eight joints (DAS28) which includes assessments of tender joint counts, swollen joint counts, ESR and patient’s global assessments. This perception is supported by previous research that shows DAS scores are often high in patients with fibromyalgia without RA [Leeb et al. 2004]. In this context DAS28 scores of 5.1 or more are considered indicative of active disease. DAS scores are particularly important in treatment decisions about disease modifying anti-rheumatic drugs (DMARDs) and biologics [Meyer et al. 2007; Fautrel et al. 2008]. If DAS scores are disproportionately high in relation to the level of inflammatory synovitis in fibromyalgic RA, the value of DAS assessments in these patients is open to question. This is a particularly cogent issue as a recent study of fibromyalgic RA by Coury et al suggested DAS28 over-estimated disease activity in these patients [Coury et al. 2009].

Patients with fibromyalgic RA were studied with three aims. Firstly to confirm that its prevalence and clinical impact in UK RA patients reflects the experience of other countries. Secondly to determine if the conventional core data set of clinical assessments in RA such as tender and swollen joint counts and ESR can be used to identify patients with fibromyalgic RA. Finally to examine the influence of fibromyalgic RA on the identification of active disease using DAS28 scores and ascertain the limitations of DAS28 in this setting.

5.1.2. Pain Thresholds in RA and Their Associations

Pain remains a dominant problem for many patients with RA, despite new treatment approaches using disease modifying drugs and biologics. Both local and central factors are likely to contribute to RA pain. Studies in experimental models of inflammatory arthritis show peripheral sensitisation induced by activation of the nociceptive system in the joints are important [Woolf et al. 1997; Inglis et al. 2005]. In addition to inflammation induced sensitisation of peripheral nociception, hyperexcitability in the spinal cord, attributed to continued stimulation by nociceptive receptors, has also been implicated [Scaible et al. 1993; Neugebauer et al. 1990]. This hyperexcitability may lead to central sensitisation [Kunz et al. 2005; Telleria-Diaz 2010]. In RA patients, increased severity of pain and reduced pressure pain thresholds are one potential consequence of central sensitisation of pain. They have previously been reported in observational studies of RA patients [Huskisson et al. 1972; Gerecz-Simon et al. 1989; Lee et al. 2009].

Central pain sensitisation is most likely in long-standing RA. It was therefore hypothesised that disease duration may affect pain thresholds. Several other potential factors could contribute to reduced pain thresholds in RA. These include high disease activity and coexistent fibromyalgia. The variability of pain thresholds in RA and the possible factors which influence them was evaluated using a cross-sectional observational study design.

5.2. OUTLINE OF PATIENTS AND METHODS

5.2.1. Patients in Initial Fibromyalgic RA and Pain Threshold Study

For the first part of the study to confirm there is evidence of fibromyalgic RA, and to define pain thresholds, prospective data was collected from 105 patients with RA as defined by the ACR criteria who were consecutive attendees in a routine outpatient clinic at King's College Hospital. All patients signed an informed consent form (Appendix 15). Demographic details of the patients recruited are summarised in Table 5.1.

Table 5:1 Patients in Initial and Replicate Studies

Variable	Initial Study (n=105)	Replicate Study (n=321)
<i>Female</i>	80 (76%)	245 (76%)
<i>Male</i>	25 (24%)	76 (24%)
<i>Age, mean years (range)</i>	60 (24-88)	60 (20-87)
<i>Disease duration, mean years (range)</i>	13 (0.08-54)	9 (0-48)
<i>Ethnicity</i> <i>Caucasian</i>	84 (80%)	281 (88%)
<i>Afro-Caribbean</i>	16 (15%)	31 (10%)
<i>Asian</i>	3 (3%)	7 (2%)
<i>Oriental</i>	2 (2%)	2 (0.6%)
<i>DMARD Therapy</i>	89 (85%)	239 (74%)
<i>Biologics</i>	20 (19%)	13 (4%)
<i>Steroid</i>	16 (15%)	72 (22%)
<i>NSAIDs</i>	56 (53%)	132 (41%)
<i>Analgesics</i>	56 (53%)	81 (25%)

The sample comprised 80 females and 25 males. Mean age was 60 years and mean disease duration 13 years. The ethnic grouping of patients recruited into the study represented Caucasian, 80%, Afro-Caribbean, 15%, Asian, 3% and Oriental, 2%. At the time of assessment, the majority of patients (93 of 105, 89%) were on second line therapy. Within this group of 93 patients, twenty patients were on biologic therapy, namely adalimumab, etanercept and infliximab. There were 78 patients on single, combination and triple DMARD therapy, which comprised 49 on methotrexate, 21 on sulphasalazine, 7 on hydroxychloroquine, 17 on leflunomide, 1 on IM-gold and 16 on prednisolone. In total 85 patients were either on NSAIDs or analgesics or both.

5.2.2. Patients in Replicate Fibromyalgic RA Study (Established RA)

Data collected from patients for a previous study was used in the replicate study. These patients were part of a study to design a patient derived disease activity score. The patients were attending outpatient clinics at four hospitals in South London. The sample comprised 245 females and 76 males. Mean age was 60 years and mean disease duration 9 years. The ethnic grouping of patients recruited into the study

represented Caucasian, 88%, Afro-Caribbean, 10%, Asian, 7% and Oriental, 0.6%. At the time of assessment, the majority of patients (244 of 321, 76%) were on second line therapy. Within this group of 244 patients, thirteen patients were on biologic therapy, namely adalimumab, etanercept and infliximab. There were 231 patients on single, combination or triple DMARD therapy, which comprised 151 on methotrexate, 44 on sulphasalazine, 17 on hydroxychloroquine, 12 on leflunomide, 15 on IM-gold, 10 on azathioprine, 9 on ciclosporin, 12 on D-penicillamine and 42 on oral corticosteroids. Thirty patients had been given either intra articular or intramuscular depomedrone. In total 245 patients were either on NSAIDs or analgesics or both.

5.2.3. Patients in Fibromyalgic Early RA Study

Data collected from patients enrolled in the early rheumatoid arthritis network (ERAN) was used for the early rheumatoid arthritis study. ERAN is a national network of rheumatologists following outcomes in patients with RA for less than two years at enrolment. The sample comprised 265 females and 130 males. Mean age was 55 years (range 18-88). The ethnic grouping of patients recruited into the study represented Caucasian, 96%, others 4%. At initiation into ERAN, 378 patients were on single or combination DMARD therapy, which comprised 17 patients on hydroxychloroquine, 148 on sulfasalazine, 173 on methotrexate, 11 on other monotherapy and 29 on combination DMARDs.

5.2.4. Assessments

5.2.4.1. Initial Study

Disease activity measures based on the EULAR/OMERACT core data set which comprises 28 tender and swollen joint counts, pain score (visual analogue scale 0-100mm), patient and physician global assessment (visual analogue scale 0-100mm), erythrocyte sedimentation rate (ESR) and health assessment questionnaire (HAQ) scores, were collected. In addition fatigue was measured using a visual analogue scale (0-100mm), duration of early morning stiffness and tender point counts (based on the ACR 18 fibromyalgic tender points). Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS).

Pain thresholds were measured using a handheld digital algometer. There have been numerous studies that evaluated the reliability and validity of this instrument in determining the pressure-pain threshold of different body tissues both in patients and controls. [Kinser et al. 2009; Wylde et al. 2011] The measurements were all done by the same investigator, minimising inter-observer error. Two measurements were taken and the mean of the two measurements was used. The algometer was applied to the right thumb nail, away from any involved joints and taking care to avoid the nail bed.

5.2.4.2. Replicate Study (Established RA)

Disease activity measures based on the EULAR/OMERACT core data set which comprises 28 tender and swollen joint counts, pain score (visual analogue scale 0-100mm), patient and physician global assessment (visual analogue scale 0-100mm), erythrocyte sedimentation rate (ESR) and health assessment questionnaire (HAQ) scores, were collected. In addition fatigue was measured using a visual analogue scale (0-100mm), duration of early morning stiffness and C-reactive protein (CRP). Quality of life was measured using the SF-36 and NHP questionnaires.

5.2.4.3. Early RA Study

The DAS28 and its constituents (28 tender and swollen joints, patient global assessment and ESR) were measured. In addition CRP, haemoglobin and the HAQ were collected at 3, 6, 12 and 24 months.

5.2.5. Analyses

5.2.5.1. Initial Study

All analyses used the Statistical Package for the Social Sciences (SPSS® 14 for Windows). Group data were reported using means (standard deviations) and ranges. The inter relationships between tender points and measures of disease activity were assessed using bivariate Spearman's correlations. To determine the factors

influencing tender points, simple regression was followed by backwards stepwise multiple regression using tender points as the dependent variable.

To determine the impact of tender points on patient outcomes, the patients were divided into two groups according to the number of positive tender points used in the diagnosis of fibromyalgia; those with 11 or more positive tender points and those with 10 or less positive tender points.

To determine if tender minus swollen joint counts could identify fibromyalgic RA as accurately as tender points, Receiver Operator Characteristic analysis was employed. Sub-groups were compared using Students t-test and frequencies using the odds ratio.

To assess the factors associated with pain threshold univariate and multivariate Ordinal logistic regression models were performed using STATA version 10 (StataCorp, Texas, 2007). As the distribution of pain thresholds was not linear, they were divided into tertiles for analysis. All continuous measures were entered into the models as continuous variables. For these analyses the crude and adjusted odds ratios with 95% confidence interval are presented, p-values are two-tailed throughout. Any variables that had a p value ≤ 0.05 in the univariate analysis were carried forward into multivariate analysis. Factors showing significant collinearity were excluded from the final model.

5.2.5.2. Replicate Study (Established RA)

To determine if the tender minus swollen joint count formula could identify fibromyalgic RA patients, the formula was applied to data from a group of patients with established disease and they were divided into two groups. The impact of 'tender minus swollen joints' was assessed by calculating means with 95% confidence intervals for the outcome measures assessed. To determine the effect of fibromyalgic RA on response to treatment, mean DAS28 scores after 6 months of treatment were compared in the two groups using independent T-test.

5.2.5.3. Early RA Study

To determine if the tender minus swollen joint count formula could identify fibromyalgic RA patients, the formula was applied to data from a group of patients with early disease and they were divided into two groups. The impact of ‘tender minus swollen joints’ was assessed by calculating means with 95% confidence intervals for the outcome measures assessed. To determine the effect of fibromyalgic RA on response to treatment, mean DAS28 scores after 24 months of treatment were compared in the two groups using independent T-test.

5.3. RESULTS

5.3.1. Tender Point Counts and Subtypes of Rheumatoid Arthritis Patients

The 105 patients assessed in the initial cohort study had a mean tender joint count (TJC) of 7.5 (SE 0.7), mean swollen joint count (SJC) of 3.6 (SE 0.3), mean patient global assessment (PGA) of 44.2mm (SE 2.5), mean DAS28 of 4.53 (SE 0.15), mean HAQ of 1.49 (SE 0.08), mean ESR of 29.6mm/hr (SE 2.2), mean early morning stiffness (EMS) of 82.4 minutes (SE 20.2), mean physician global assessment (PhysGA) of 23.1mm (SE 1.5), mean pain VAS of 49.8mm (SE 2.8), mean fatigue VAS of 54.7mm (SE 2.7), mean tender points of 4.4 (0.5) and mean pain threshold of 331.8 KPa (SE 18.8).

Tender point counts showed correlations of moderate significance with tender joint counts (0.71), DAS28 (0.64), fatigue (0.52), patient global assessments (0.49), pain (0.47), HADS depression (0.48), pain threshold (-0.55), HAQ (0.51), early morning stiffness (0.33) and HADS anxiety (0.39); $p < 0.01$ in all cases. They also showed correlations of minimal significance with physicians global assessments (0.22; $p < 0.05$). They were not correlated with ESR (0.11), swollen joint counts 0.18), age (0.04) and disease duration (-0.004).

Stepwise backwards multiple regression analysis using tender point counts as the dependent variable showed three variables explained 61% of the variation. Tender joint counts had the strongest association, and these were followed by pain threshold (negative association) and the HADS depression score (Table 5.2).

**Table 5:2 Regression Analysis of Factors Influencing Tender Point Counts
Initial Study**

Tender Point Counts ($R^2 = 0.61$)		
<i>Variable</i>	<i>Coefficients (95% CI)</i>	<i>Significance</i>
Tender joint counts	0.38 (0.273, 0.483)	p=0.001
Pain Threshold	-0.005 (-0.009, -0.002)	p=0.005
HADS Depression	0.23 (0.04, 0.42)	p=0.016
<i>Excluded variables</i>		
HADS Anxiety, HAQ, Pain, PGA, ESR, Fatigue, Physician Global Assessment		

5.3.1.1. Prevalence of Fibromyalgic RA

18/105 (17%) of patients in the initial cohort and 12/100 (12%) of patients in the replicate cohort had 11 or more tender points and met the criteria for fibromyalgic RA.

5.3.1.2. Identifying Fibromyalgic RA Using Tender Joint Counts

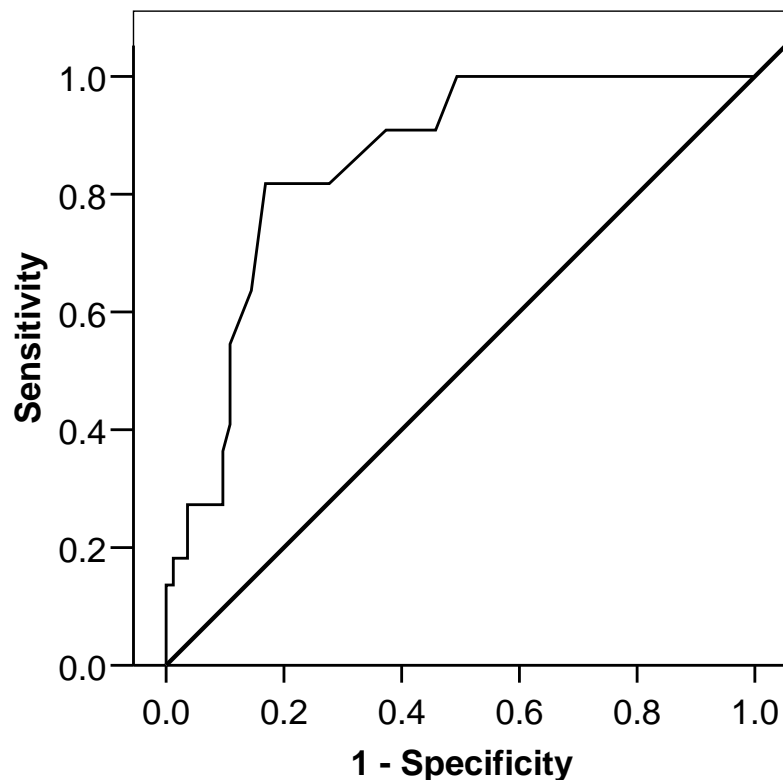
In the initial cohort tender point counts correlated strongly with tender joint counts (Pearson's correlation $r=0.74$) and tender minus swollen joints ($r=0.70$); tender/swollen joints could not be used as it would mean dividing by zero in patients with no swollen joints. To take into account patients with very active synovitis having high numbers of both tender and swollen joints tender minus swollen joints were evaluated in more detail.

Receiver operator characteristic (ROC) analysis showed the area under the curve using tender minus swollen joints to identify fibromyalgic RA patients defined by tender point count scores was 0.86. Tender minus swollen joint counts of ≥ 7 predicted the presence of ≥ 11 tender points with 83% sensitivity and 80% specificity. (Figure 5.1) The number of patients with 11 or more tender point counts who also had tender minus swollen joint counts of ≥ 7 was 15 (83%), meaning 3 patients had 11 or more tender point counts but less than 7 tender minus swollen joint counts. Of the 87 patients who had less than 11 tender point counts 17 (19.5%) had 7 or more tender minus swollen joint counts. Thirteen of the 17 patients who had 7 or more tender minus swollen joint counts had 5 or more tender points and 5 had 9 or 10

tender points. This gave the tender minus swollen joints count a negative predictive value of 96%.

In the replicate cohort tender point counts correlated with tender joint counts ($r=0.78$) and tender-swollen joint counts ($r=0.77$ in both cases). ROC analysis showed the area under the curve using tender minus swollen joints to identify fibromyalgic RA patients defined by tender point count scores was 0.94. Tender minus swollen joint counts of ≥ 7 predicted the presence of ≥ 11 tender points with 72% sensitivity and 98% specificity.

**Figure 5:1 ROC of “Tender Minus Swollen Joint Counts”
Ability to Identify Patients with 11 or More Tender Point Counts**



“Tender minus swollen joint counts” ≥ 7 and tender point counts ≥ 11
Sensitivity = 83% (95% CI 58%, 96%), Specificity = 80% (95% CI 71%, 88%),
Efficiency = 81% (95% CI 72%, 0.88%)

5.3.1.3. Clinical Impact of Fibromyalgic RA

Patients with fibromyalgic RA identified by high tender point scores (initial cohort) or high tender minus swollen joint counts (initial cohort and clinical practice cohort)

had higher tender joint counts, patient global assessments, DAS28 scores, pain scores, fatigue and HAQ (Table 5.3). However, their swollen joint counts were similar to those of other RA patients.

5.3.1.4. Fibromyalgic RA and Active Disease

The impact of fibromyalgic RA, assessed by tender point counts of 11 or more on the definition of active disease was evaluated by combining data from the initial and replicated cohorts.

Most patients with fibromyalgic RA had DAS28 scores of 5.1 or more compared to only a minority of other patients; the odds ratio (OR) and 95% confidence intervals (CI) for having active disease by DAS28 criteria with fibromyalgic RA was 14.3 (5.5, 37.1). The same situation occurred if the DAS28 was replaced by CDAI, taking 22 or more as being active disease with fibromyalgic RA patients having an increased likelihood of being classified as active (OR 17.2; 95% CI 6.1, 48.5).

By contrast using more conventional assessments based on reaching predefined numbers of tender and swollen joints and a high ESR showed fewer patients with fibromyalgic RA patients had active disease. Using ≥ 3 or more tender and swollen joints and an ESR of ≥ 28 showed a non-significant increase in active disease in patients with fibromyalgic RA (OR 1.75; 95%CI 0.72, 4.3). This difference is shown in the Figure 5.2. There were similar findings with ≥ 6 or more tender and swollen joints and an ESR of ≥ 28 (OR 2.6; 95% CI 0.88, 7.6).

5.3.2. Comparison of Different Groups of Rheumatoid Arthritis Patients

5.3.2.1. Early Rheumatoid Arthritis

The same criteria were applied to a cohort of patients with early disease, to determine if the formula could be applied to RA patients at different stages of disease duration to identify this specific subset of patients. Data that had been collected for the ERAN study was used. The patients were collected from various centres across the UK, provided they had a disease duration of 2 years or less.

After applying the tender minus swollen joint formula to this cohort of patients, similar results were obtained. Of the 394 patients studied, 67 patients had tender joint minus swollen joint counts of 7 or more and 327 patients with less than 7. The patients with tender joints minus swollen joints ≥ 7 had significantly higher tender joints (17), DAS28 scores (5.9) and HAQ scores (1.5). There was no difference in swollen joint counts or ESR. (Table 5.4)

Table 5:3 High Tender Point Counts and Tender Minus Swollen Joint Counts

	Initial Study				Replicate study	
	Tender points ≥11 (<i>n</i> =22)	Tender points <11 (<i>n</i> =83)	Tender joints minus swollen joints ≥7 (<i>n</i> =32)	Tender joints minus swollen joints <7 (<i>n</i> =73)	Tender joints minus swollen joints ≥7 (<i>n</i> =71)	Tender joints minus swollen joints <7 (<i>n</i> =250)
<i>Pain VAS</i>	71 (61, 82)	45 (39, 51)	71 (63, 78)	41 (34, 47)	63 (58, 68)	43 (40, 46)
<i>Fatigue VAS</i>	82 (72, 91)	50 (44, 56)	72 (63, 80)	47 (41, 53)	62 (56, 68)	46 (43, 50)
<i>Tender joints</i>	17 (14, 21)	6 (4, 7)	16 (14, 18)	4 (3, 5)	18 (16, 19)	5 (4, 5)
<i>Swollen joints</i>	4 (2, 6)	4 (3, 4)	3 (2, 4)	4 (3, 4)	6 (5, 7)	5 (4, 5)
<i>ESR</i>	39 (22, 55)	27 (23, 32)	33 (22, 43)	28 (24, 32)	32 (27, 38)	33 (30, 36)
<i>Patient global VAS</i>	66 (55, 77)	40 (34, 46)	61 (53, 68)	37 (31, 42)	63 (58, 69)	46 (43, 40)
<i>DAS28</i>	6.0 (5.5, 6.5)	4.3 (3.9, 4.6)	5.7 (5.3, 6.1)	4.0 (3.7, 4.3)	6.1 (5.8, 6.3)	4.4 (4.2, 4.5)
<i>HAQ</i>	2.0 (1.8, 2.3)	1.4 (1.2, 1.5)	1.9 (1.6, 2.1)	1.3 (1.2, 1.5)	1.9 (1.7, 2.1)	1.4 (1.3, 1.5)

Values for each assessment are given with 95% confidence intervals in brackets

**Figure 5:2 Fibromyalgic RA and Assessments of Active Disease
Initial and Replicate Cohorts Combined.**

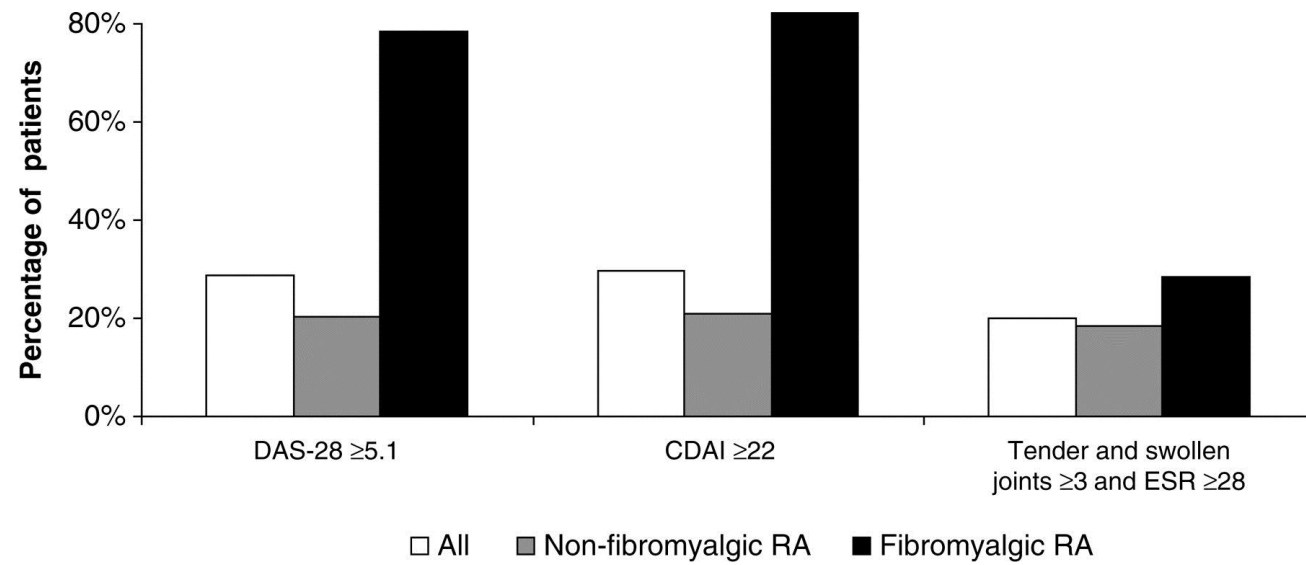


Table 5:4 High “Tender Minus Swollen Joint Counts” In Early RA

	Tender joints minus swollen joints ≥ 7 (n=67)	Tender joints minus swollen joints < 7 (n=327)
<i>Tender joints</i>	17 (16, 18)	6 (6, 7)
<i>Swollen joints</i>	5 (4, 6)	6 (6, 7)
<i>ESR</i>	37 (30, 44)	31 (28, 34)
<i>DAS28</i>	5.9 (5.6, 6.2)	4.6 (4.4, 4.8)
<i>HAQ</i>	1.5 (1.3, 1.7)	1.0 (0.9, 1.1)

5.3.2.2. Treatment Effects

To determine if patients with fibromyalgic RA as defined by tender minus swollen joint counts of 7 or more respond to treatment in a similar fashion to other patients changes in DAS28, tender joints, swollen joints and ESR following treatment were examined in patients with established disease and also patients with early disease.

5.3.2.3. Established Rheumatoid Arthritis

Patients in the established RA study who had assessments following six months of treatment with either DMARDs or biologics were included. A total of 62 patients had data before and after six months of treatment. The tender minus swollen joint count formula was again applied to this group and 16 patients had tender minus swollen joint counts of 7 or more and 46 patients had less than 7. Following treatment for 6 months there was no significant difference in mean improvements of tender joints, swollen joints, ESR or DAS28 between the two groups. Although there were greater numerical improvements in tender joints in the patients with tender minus swollen joints of 7 or more and greater numerical improvements in ESR in the tender minus swollen joints of less than 7. (Table 5.5) However, the mean DAS28 score for the patients with tender minus swollen joint counts of 7 or more was still significantly higher than those with less than 7 tender minus swollen joints (5.64 SD 1.56 vs. 4.44 SD 1.59, $p=0.013$)

Table 5:5 High “Tender Minus Swollen Joint Counts” and Treatment Changes DMARDS or Biologics in Established Disease; Mean Improvement (95% CI)

	Tender joints minus swollen joints ≥ 7 (n=16)	Tender joints minus swollen joints < 7 (n=46)
<i>Tender joints</i>	7 (2, 12)	1 (0, 3)
<i>Swollen joints</i>	2 (0, 4)	3 (1, 5)
<i>ESR</i>	6 (8, 20)	22 (13, 32)
<i>DAS28</i>	1.2 (0.5, 2.0)	1.2 (0.7, 1.7)

5.3.2.4. Early Rheumatoid Arthritis (ERAN)

All the patients in the ERAN study had assessments at 6, 12 and 24 months following treatment with DMARDS or biologics. As stated previously, 67 patients in this data set had tender joint minus swollen joint counts of 7 or more. After 24 months of treatment, there was a significantly greater improvement in the number of tender joints in the group with tender joint minus swollen joint counts of 7 or more, otherwise there was no significant difference in improvement in swollen joints, ESR or DAS28 between the two groups. (Table 5.6) However, after 24 months of treatment the mean DAS28 score for the patients with tender minus swollen joint counts of 7 or more was still significantly higher than those with less than 7 tender minus swollen joints (4.37 SD 1.52 vs. 3.64 SD 1.55, $p=0.012$).

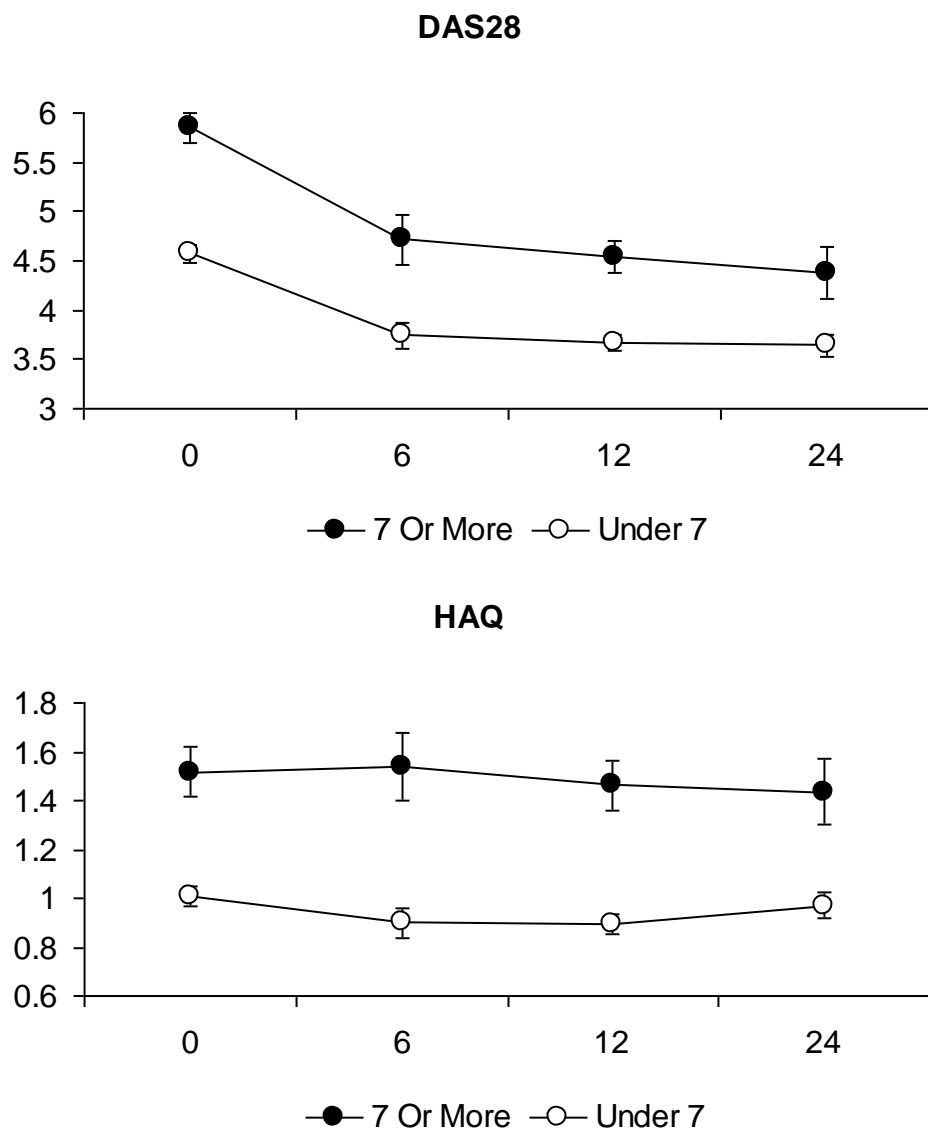
Table 5:6 High “Tender Minus Swollen Joint Counts” on Treatment Changes DMARDS in Early Disease

	Tender joints minus swollen joints ≥ 7 (n=67)	Tender joints minus swollen joints < 7 (n=327)
<i>Tender joints</i>	7 (6, 9)	2 (1, 2)
<i>Swollen joints</i>	2 (1, 3)	3 (2, 4)
<i>ESR</i>	14 (8, 20)	9 (7, 12)
<i>DAS28</i>	1.3 (0.9, 1.7)	0.9 (0.7, 1.1)

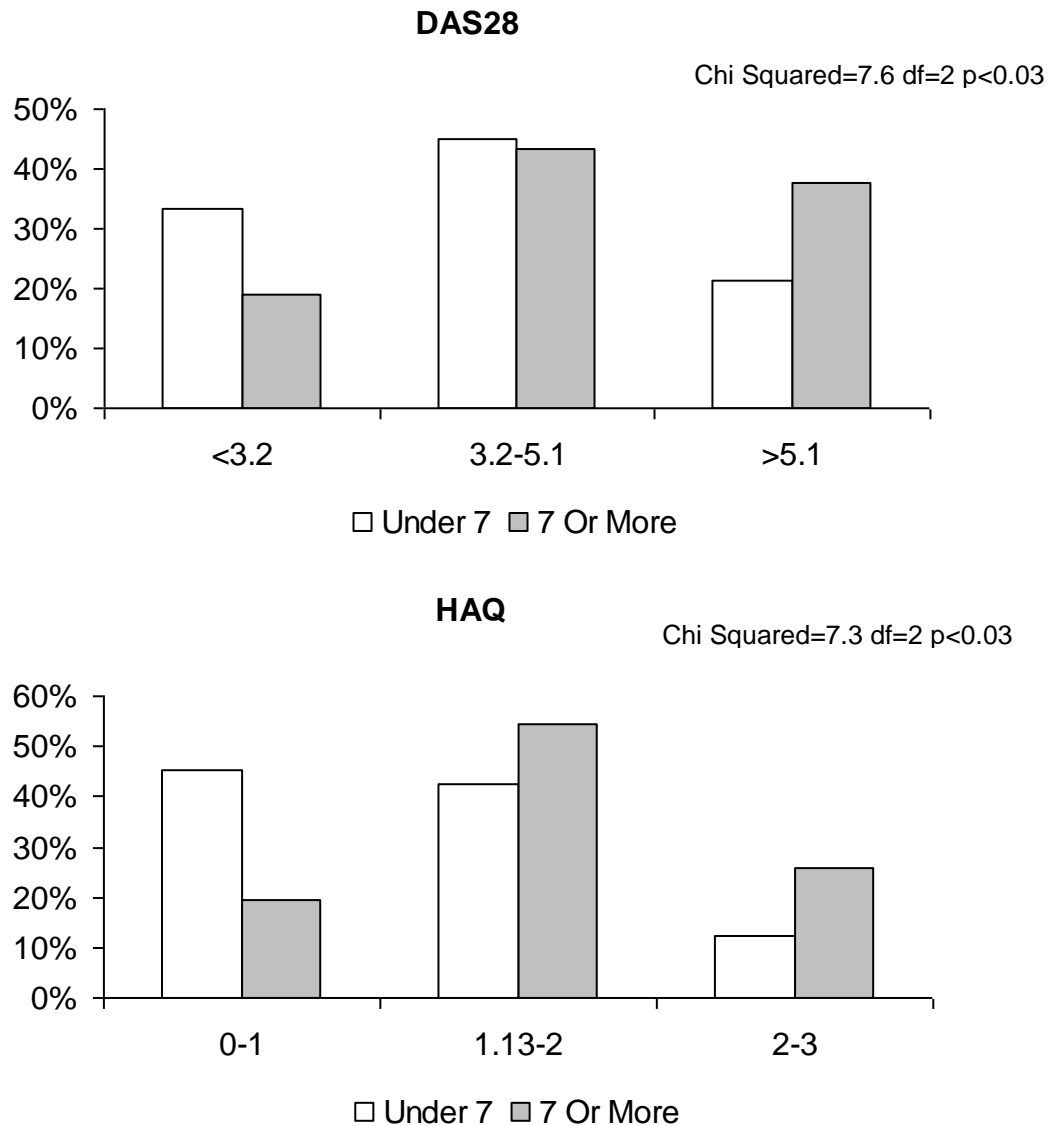
To compare the change in DAS28 and HAQ scores between the two groups of patients with similar treatment regimes, patients who were treated with either methotrexate or sulphasalazine only were included in the analysis. There were

improvements in DAS28 scores in both groups of patients at 6, 12 and 24 months, although mean DAS28 scores at 24 months remained higher in the group with 7 or more tender minus swollen joint counts (4.56 SD1.52 vs. 3.64 SD 1.42, $p=0.002$). There were minor but significant improvements in HAQ after 24 months of treatment in both groups but HAQ remained significantly higher in the group with 7 or more tender minus swollen joint counts (1.44 SD 0.75 vs. 0.98 SD 0.73, $p=0.002$). (Figures 5.3 and 5.4)

Figure 5:3 “Tender Minus Swollen Joint Counts”, DAS28 and HAQ Scores Early RA Patients Treated With Methotrexate or Sulfasalazine (Mean and SE)



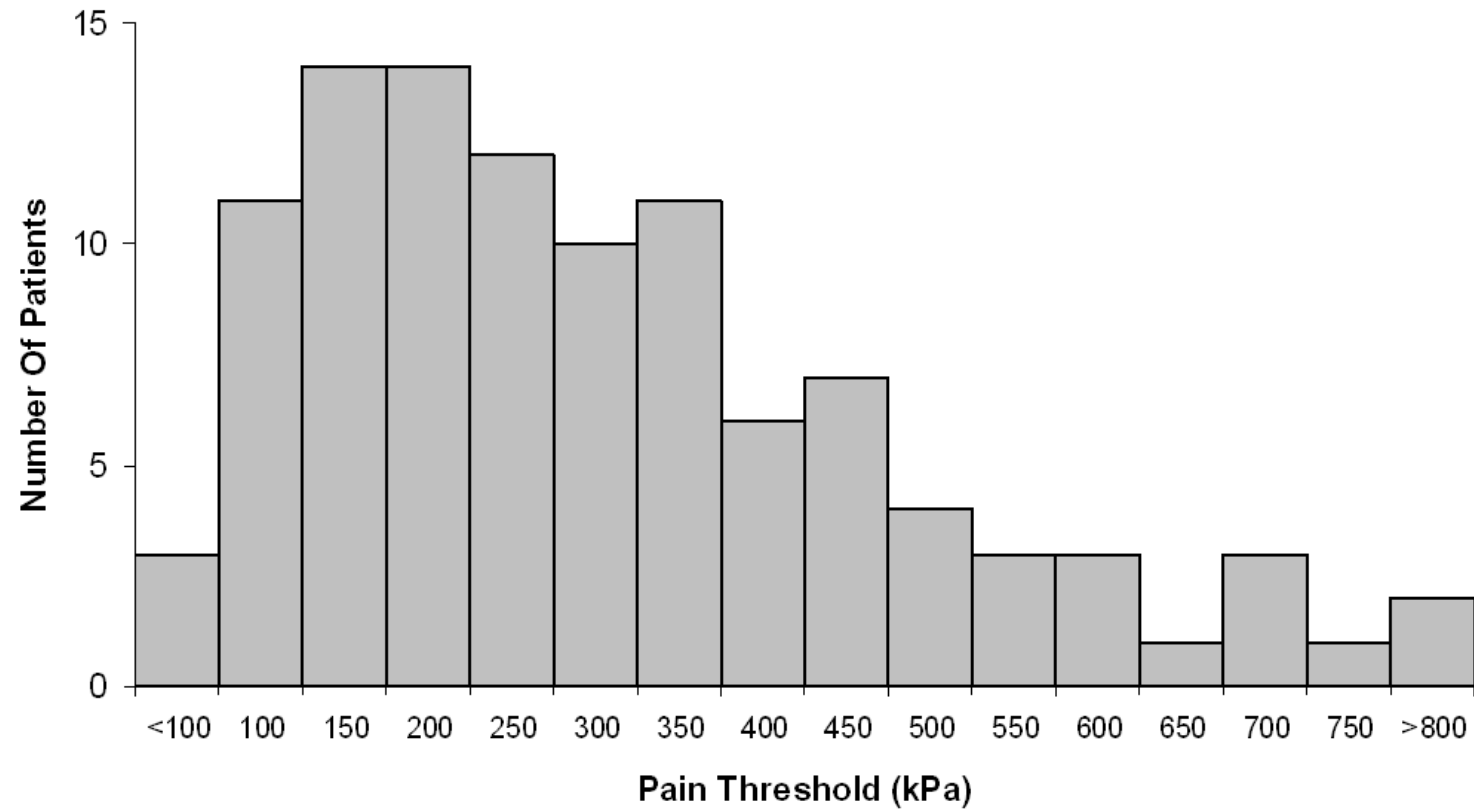
**Figure 5:4 “Tender Minus Swollen Joint Counts” DAS28 and HAQ Levels
Early RA Patients who Initially had DAS28 \geq 5.1 after 24 Months of Treatment
with Methotrexate or Sulfasalazine**



5.3.3. Pain Thresholds and its Associations

5.3.3.1. Distribution of Pain Thresholds

The median pain threshold was 289 with an interquartile range of 189-434 and upper and lower levels of 67 and 1123 kPa. The distribution of pain thresholds (Figure 5.5) showed a broad range with a substantial upper “tail” of high pain thresholds

Figure 5:5 Distribution of Pain Thresholds in RA

5.3.3.2. Relationship to Disease Activity and Associated Clinical Variables

The relationships to disease activity and demographic assessments were evaluated using Spearman's correlations (Table 5.7). Pain threshold showed high correlations ($R>0.4$) with tender point counts, tender joint counts, fatigue (VAS) and HAQ; moderate correlations ($R=0.2-0.4$) with pain (VAS), HADS depression and anxiety, patient global assessments, disease duration and age; and no correlation ($R<0.2$) with swollen joint counts, physician global assessment, ESR and early morning stiffness.

Table 5:7 Pain Thresholds and Clinical and Demographic Variables

Variable	Spearman's Correlation	Significance
Age	-0.19	0.046
Disease Duration	-0.21	0.031
Early Morning Stiffness	-0.18	0.071
ESR	-0.61	0.504
FACIT	0.31	0.002
Fatigue (VAS)	-0.44	0.000
HADs-A	-0.32	0.002
HADS-D	-0.35	0.000
HAQ	-0.44	0.000
Pain VAS	-0.34	0.000
Patient Global Assessment (VAS)	-0.33	0.001
Physicians Global Assessment (VAS)	-0.10	0.328
Sex	-0.15	0.116
Swollen Joint Counts	-0.04	0.698
Tender Joint Counts	-0.44	0.000
Tender Points	-0.55	0.000

The relationship of tender point counts and disease duration to pain thresholds were evaluated in detail (Figure 5.6). Pain thresholds were lower in patients with tender point scores of ≥ 11 ($p < 0.001$ Mann Whitney test). They were also lower in patients with disease durations ≥ 10 years ($p = 0.027$ Mann Whitney test).

5.3.3.3. Regression Analysis

Ordinal logistic regression evaluated pain threshold tertiles to disease activity and other clinical measures. Adjusted odds ratios showed tender point counts and disease duration were independently associated with pain thresholds (Table 5.8). In the adjusted model age did not retain significance suggesting that it is disease duration and not age that is the dominant factor. Tender joint counts and patient global assessments showed significant collinearity with tender point counts and pain and were excluded from the adjusted model. In the multivariable model fatigue (VAS or FACIT-F), anxiety, depression and disability (HAQ) were not associated with pain thresholds.

Figure 5:6 Pain Thresholds, Tender Points and Disease Duration
Median and IQR Shown In Box-Plots

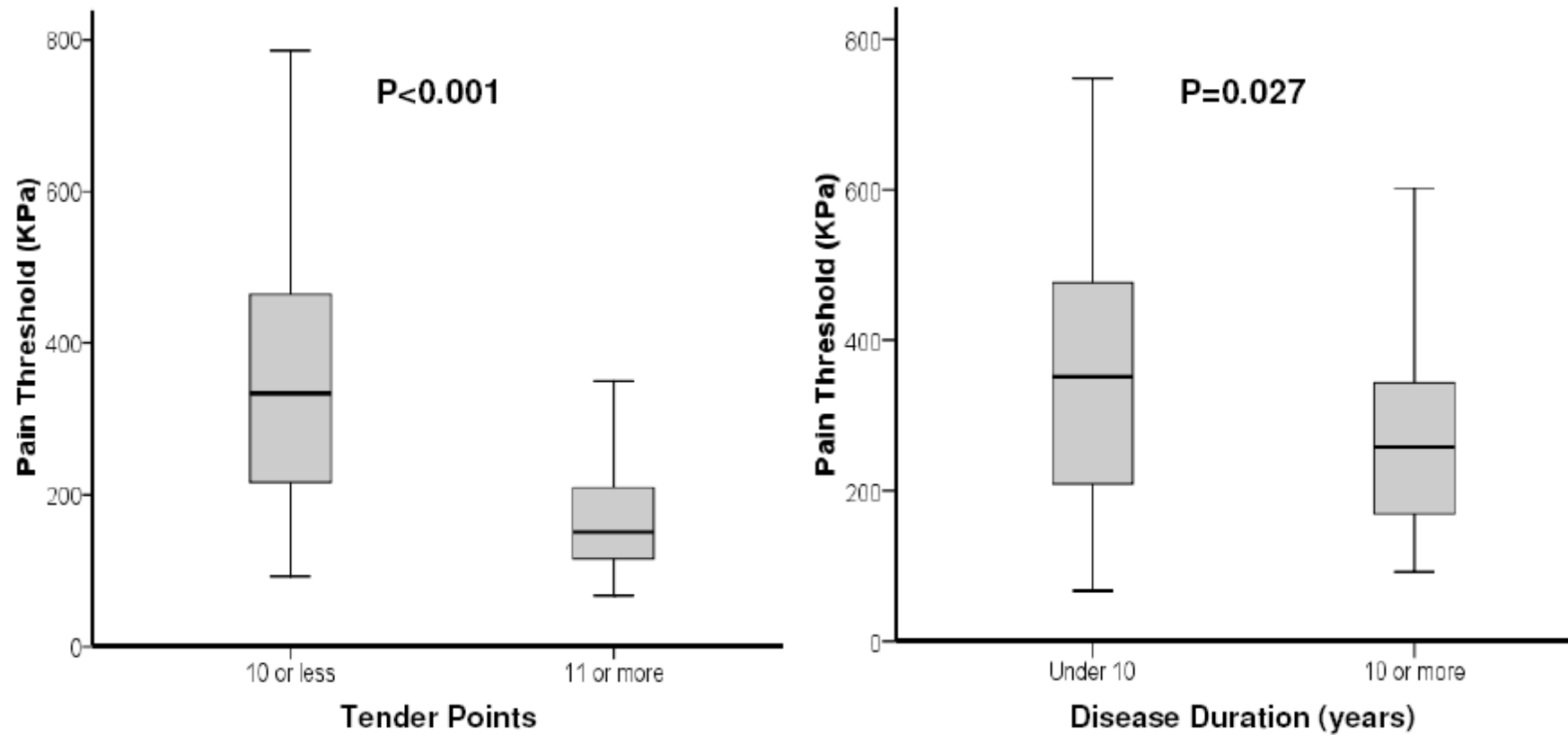


Table 5:8 Regression Analysis of Factors Associated with Pain Threshold
Crude and Adjusted Models are Shown

Factor	Crude OR (95% CI)	P	Adjusted OR(95%CI)	P
Age	0.97 (0.94,0.99)	0.015	0.97 (0.94, 1.01)	0.16
Disease Duration	0.97 (0.94,1.00)	0.037	0.95 (0.91, 1.00)	0.04
Pain (VAS)	0.98 (0.97,0.99)	0.002	0.99 (0.97, 1.01)	0.38
Number Of Tender Points	0.78 (0.71,0.86)	<0.001	0.75 (0.65, 0.86)	<0.001
Fatigue (VAS)	0.97 (0.96,0.99)	<0.001	0.98 (0.96, 1.00)	0.15
Health Assessment Questionnaire	0.39 (0.23,0.69)	0.001	1.19 (0.56, 2.56)	0.64
Erythrocyte Sedimentation Rate (ESR)	0.98 (0.96, 1.00)	0.035	1.00 (0.98, 1.03)	0.83
FACIT-F	1.04 (1.01,1.08)	0.011	-	-
Tender Joint Count	0.88 (0.82,0.93)	<0.001	-	-
Patient Global Assessment (VAS)	0.98 (0.96,0.99)	0.003	-	-
HADS Depression	0.89 (0.81,0.99)	0.028	-	-
HADS Anxiety	0.92 (0.83,1.01)	0.064	-	-
Duration of Morning Stiffness (mins)	1.00 (0.99,1.00)	0.076	-	-
White vs. Other Ethnic Groups	1.52 (0.62,3.74)	0.360	-	-
Swollen Joint Count	0.96 (0.86,1.07)	0.428	-	-
Male vs. Female	0.67 (0.28,1.61)	0.373	-	-

Explanatory Note: The adjusted odds ratio excluded EMS, HADS anxiety, ethnicity, swollen joint count and gender as they showed no significant relationship with pain thresholds at the 0.05 level. HADS Depression, tender joint count, patient global assessment, fatigue VAS, FACIT-F and HAQ were all significantly correlated with pain threshold. However, many were also highly correlated with each other (eg tender point counts and tender joint counts $r=0.71$). Those variables which showed strong collinearity with each other were excluded. Where strong collinearity existed statistical and clinical assessments were used to decide which variables to include (for example tender points counts were chosen over tender joint counts).

5.4. DISCUSSION

These findings confirm previous reports that 10–20% of RA patients attending specialist units have fibromyalgic RA. All centres evaluating fibromyalgic RA report similar frequencies in patients attending specialist centres. Bliddal and Danneskiold-Samsøe [Bliddal et al. 2007] have highlighted the importance of chronic widespread pain in rheumatic diseases including RA, pointing out that not all patients meet accepted diagnostic tender point criteria of ≥ 11 for diagnosing fibromyalgia. Recent work from Ranzolin et al, [Ranzolin et al. 2009] also showed that high DAS28 scores are common in patients with fibromyalgia and RA, and Wolfe [Wolfe 2009] suggested the term ‘fibromyalginess’ applied to such patients whom he considered to have polysymptomatic distress. The balance of evidence suggests that there is a subset of RA patients with a fibromyalgic phenotype who have high pain levels unrelated to synovial inflammation, high fatigue scores and more disability with high HAQ scores. In other rheumatic diseases, particularly connective tissue disorders such as SLE, some studies report limited evidence of an increase in fibromyalgic symptoms [Wolfe et al. 2009] whereas other studies show that fibromyalgic features are commonplace [Gladman et al. 1997]. When interpreting these data it must be remembered that this is based on relatively small numbers of patients from one department although estimates are similar to other studies from different centres and patient characteristics are similar. [Wolfe et al. 1983; Wolfe et al. 1984; Wolfe et al. 2011; Kapoor et al. 2011] Nevertheless it is important not to simply label these patients as there is evidence from previous studies that disease severity is similar to non-fibromyalgic RA patients [Wolfe et al. 1984] and disease activity should be treated appropriately; however, identifying these patients with apparently worse outcomes may be beneficial to ensure that all aspects of their care are optimised.

In order to identify these RA patients with apparent worse outcomes we devised a way to screen for these patients using a conventional core data set. In our study these patients had disproportionately high tender joint counts, and could be identified by examining tender minus swollen joint counts. A subsequent study has used our suggestions for identifying fibromyalgic RA using tender minus swollen joint counts [Kapoor et al. 2011] and using this method found that 15% of patients had

fibromyalgic RA as defined using tender minus swollen joint counts but only 6% of patients had fibromyalgic RA as defined using conventional tender points. It is possible that using tender minus swollen joint counts may overestimate the prevalence of fibromyalgic RA. Research from Wolfe and Michaud [Wolfe et al. 2009] suggests that fibromyalgia and by implication fibromyalgic RA are one end of a spectrum. Consequently using cut-off points of ≥ 11 tender points or tender minus swollen joint count of ≥ 7 over simplifies a complex situation. One crucial question is whether it is appropriate to divide patients into those with or without fibromyalgic RA—the evidence suggests that it is better to consider fibromyalgic features as a continuum rather than a diagnosis that is either present or absent. Indeed Wolfe et al [Wolfe et al. 2011] showed that up to approximately 20% of RA patients may develop fibromyalgic symptoms at some point during their disease. A second related question is whether in this context fibromyalgia is a separate associated disease or a symptom complex; the latter approach is favoured. However, irrespective of these questions, patients with high tender joint counts but few swollen joints seem to differ from the majority of patients with relatively equal numbers of tender and swollen joints. Such patients with a pattern of fibromyalgic RA will still need conventional treatment with DMARDs to suppress inflammation but are likely to need other approaches to fully control their symptoms such as exercise and psychological treatments.

Using DAS-28 ≥ 5.1 to define active RA has the benefits of simplicity and reproducibility. However, these results show that it may overestimate the activity of patients with fibromyalgic RA [Atzeni et al. 2011]. Using CDAI, which has been shown to perform in a similar fashion in RA as the DAS28, [Dejaco et al. 2011] as an alternative does not change this over-representation. The explanation for this effect is the way in which these indices handle joint counts with equal weighting given to the numbers of tender joints no matter how high these are. The classic entry criteria for trials involve patients having high swollen joint counts [Kingsley et al. 2005] and therefore avoid entering patients with a purely fibromyalgic pattern of disease. These results suggest that there are strong arguments in favour of using conventional trial entry criteria, such as having three or more tender and swollen joints and an elevated ESR, rather than only concentrating on DAS28 scores. Some patients with many tender points and high tender joint counts who have features of fibromyalgic RA and

DAS-28 ≥ 5.1 also have evidence of synovial inflammation with high swollen joint counts. Assessing disease activity in fibromyalgic RA is clearly challenging and complex [Mäkinen et al. 2009]. However, using DAS28 ≥ 5.1 as the sole criterion to define active RA is too simple and will misclassify a substantial number of patients. Such summary measurements need to be tempered with additional clinical assessments to enable patients to receive the optimal treatment they need [Deighton et al. 2008; Ton et al. 2012].

When looking at the effect of treatment on patients with fibromyalgic RA both patients with early and established disease had improvements across most variables of the DAS28, however, despite treatment these patients still had significantly higher DAS28 scores following treatment compared to those patients who did not have fibromyalgic RA. The changes in DAS28 with treatment are mirrored by the changes in HAQ with treatment in the same group of patients. Again like the DAS28 scores, HAQ scores remain higher in those patients with fibromyalgic RA compared to those without fibromyalgic RA despite treatment with conventional DMARDs. These findings add weight to the argument that other treatments besides conventional treatments are needed in order to reduce DAS28 scores and disability as measured by the HAQ.

Pain thresholds vary substantially in RA patients and are affected by many clinical variables. The dominant factors are high tender point counts, reflecting the presence of fibromyalgic RA [Wolfe et al. 2004; Ranzolin et al. 2009], and prolonged disease duration, which probably reflects central sensitisation. Lee et al, [Lee et al. 2009] highlighted the importance of sleep, although they found no link to disease duration, in the patients they studied.

“Fibromyalgic RA”, defined by ≥ 11 tender points, affects 10-20% of RA patients; most of these patients had low pain thresholds. The association of low pain threshold with disease duration is likely to have a different explanation. It was particularly marked in patients with RA of more than ten years duration. This finding suggests that over time the burden of inflammation in RA causes not only progressive joint damage and functional decline but also can lead to persistence of pain. It implies that

chronic RA inflammation results in persisting nociceptive stimulation, resulting in central sensitisation and reduced pain thresholds.

This study has a number of limitations. It was relatively small, it was at a single time point and the impact of treatment was not investigated. Nevertheless, the results in this thesis highlight a potentially important factor in the perpetuation of RA pain.

Early and intensive treatment which minimises inflammation is likely to reduce central sensitisation and minimise long-term RA pain. Traditional analgesics may have limited value in patients for whom pain remains a problem despite apparent control of their synovitis. Their pain management should focus on treatments that are effective in the presence of central sensitisation.

CHAPTER 6. UNDERSTANDING TREATMENT DECISIONS

6.1. INTRODUCTION

In the UK and Europe the DAS28 score is the most widely used measure of disease activity although it is not widely used in the US, where there is no agreed gold standard for assessing disease activity in clinical practice. [Furst et al. 2007] Treatment strategies that are currently advocated in RA are to treat the disease early and aggressively with either combination drugs or rapid escalation of monotherapy to try and achieve good control of disease activity and prevent long term damage and disability. [NICE, CG79. 2009; Haraoui et al. 2011; Smolen et al. 2010; Bykerk et al. 2011] The DAS28 is of particular importance in the UK as to qualify for biologic therapy on the NHS you must have active disease as defined by a DAS28 score of 5.1 or greater on two occasions as well as failing at least two DMARDs. [NICE, TA130. 2007]

As treatments have improved over the years with the introduction of early and combination therapies and biologics, it is reasonable to assume that disease activity in RA has fallen over time. There are also studies which have suggested that RA itself may becoming a milder disease [Welsing et al. 2005], although it is not clear if this is the case and that the improvements seen coincide with different treatment strategies.

Despite clear recommendations regarding treatment in RA; patients continue to have active disease and only a relatively small proportion of patients receive combination therapies despite having evidence of active disease [Kiely et al. 2011]. This study by Kiely et al for ERAN, (Early Rheumatoid Arthritis Network) of routine practice in the UK of an inception cohort of early RA patients followed over time showed that if you had a DAS28 score indicating moderate disease (DAS28 3.2 to 5.1) at the end of the first year of treatment following diagnosis, then the likelihood of achieving a low disease activity score (<3.2) at years 2 and 3 is poor.

It is unclear what prompts treatment changes for some patients who have active disease and not for others. There may be other factors which influence DAS28 scores such as fibromyalgic RA [Pollard et al. 2010] that affect treatment decisions and clinicians may use clinical judgement in these situations rather than specifically

relying on the DAS28. A recent study has suggested that the decisions which lead to an escalation in treatment differ between patients and physicians. [van Hulst et al. 2011]

This study looked at disease activity over a 13 year period between 1997 and 2010 at five different time points. There were five different cohorts of patients undergoing routine clinical care. It assessed whether there was evidence of a change in disease activity over time and also looked at changes in DMARD therapy in line with treatment guidelines as they were produced. It also looked at the impact of fibromyalgic RA over time. Secondly it looked at a further cohort of patients undergoing routine clinical care to explore the treatment changes that were instituted according to DAS28 score and evaluated the effect of fibromyalgic RA on the DAS28 as well as treatment decisions.

6.2. OUTLINE OF PATIENTS AND METHODS

6.2.1. Patients

6.2.1.1. Temporal Changes Study

All patients met the 1987 ACR criteria for RA. They comprised in total 987 patients. Data were collected from five different time points; 1997, 2003, 2006, 2008 and 2010. There were five separate cohorts of patients. All patients were attending rheumatology outpatient departments from two hospitals within South East London, either a large teaching hospital or a district general hospital. These patients were receiving routine clinical care.

6.2.1.2. Treatment Changes Study

The patients in the treatment changes study all met the 1987 ACR criteria for RA and were attending outpatient departments in South East London in either a large teaching hospital or a district general hospital. Patients were consecutive attendees at the rheumatology departments in each hospital. This was a cross-sectional study with data collected over a two year span. Patients were receiving routine clinical care. (Table 6.1)

6.2.2. Assessments

6.2.2.1. Temporal Changes Study

Demographic data was collected for each patient, including age, sex, and disease duration. All patients had measures of disease activity documented, including the DAS28 and its constituents (tender joint count, swollen joint count, ESR and patient global assessment). All DMARDs, biological therapies, steroids and NSAIDs being taken by each patient were documented. Patients with fibromyalgic RA were identified by the methods recommended by Pollard et al in 2010; patients who had ≥ 7 tender minus swollen joints.

6.2.2.2. Treatment Changes Study

Demographic data were collected for each patient, including age, sex, ethnicity and disease duration. All patients had measures of disease activity documented, including the DAS28 and its constituents (tender joint count, swollen joint count, ESR and patient global assessment). Note was made of each patient's current DMARD therapy. At each visit note was made of any treatment change, including whether it was a new DMARD that was given or an increase in current DMARD, biological therapy was commenced or if steroids were given (oral or intramuscular). Patients with fibromyalgic RA were identified by the methods recommended by Pollard et al in 2010; patients who had ≥ 7 tender minus swollen joints.

6.2.3. Analyses

6.2.3.1. Temporal Changes Study

Data analysis was done by the Statistical Package for the Social Sciences (SPSS for Windows 16). Simple descriptive analyses were applied to all data (Table 6.1). Mean DAS28 scores with standard deviations and standard errors were calculated for each time period. This was repeated for all the DAS28 constituents (tender joint count, swollen joint count, patient global assessment and ESR). Patients were divided by DAS28 categories into four groups: Remission ($\text{DAS28} < 2.6$), low disease activity ($\text{DAS28} 2.6$ to < 3.2), moderate disease activity ($\text{DAS28} 3.2$ to < 5.1) and high disease activity ($\text{DAS28} \geq 5.1$). The percentage of patients in each DAS28 category was calculated for each time point. The patients were also grouped into fibromyalgic and

non-fibromyalgic RA. Mean DAS28 scores for fibromyalgic and non-fibromyalgic patients were calculated including standard deviation and standard errors.

6.2.3.2. Treatment Changes Study

Data analysis was done using the Statistical Package for the Social Sciences (SPSS for Windows 16). Simple descriptive analyses were applied to all data. Patients were divided by DAS28 categories into four groups: Remission ($\text{DAS28} < 2.6$), low disease activity ($\text{DAS28} \geq 2.6$ to < 3.2), moderate disease activity ($\text{DAS28} \geq 3.2$ to < 5.1) and high disease activity ($\text{DAS28} \geq 5.1$). For each category the percentage of patients who had a treatment change was calculated. In those with high disease activity ($\text{DAS28} \geq 5.1$) the rate of treatment change was examined further and patients were divided further into five groups according to DAS28. These groups comprised DAS28 of 5.1-5.5, DAS28 of 5.5 to 6.0, DAS28 of 6.0-6.5, DAS28 of 6.5-7.0 and those with a DAS28 of over 7.0. Again percentages of patients who had a treatment change were calculated for each group. The percentage for each type of treatment change was also calculated for each DAS28 category.

To determine what influenced treatment changes binary regression was performed for each variable (univariate analysis) and reported as odds ratios (as there were categorical and continuous variables). Any variable which showed significance ($p \leq 0.05$) at this level was carried forward into the multivariate analysis and the odds ratios are reported. Two models were analysed, firstly DAS28 was used as a measure of disease activity and its constituents were excluded. In the second model the four constituents of the DAS28 (tender joint count, swollen joint count, ESR and patient global assessment) were included and the DAS28 composite measure was excluded.

Patients were categorised as fibromyalgic and non-fibromyalgic RA (tender minus swollen joint counts of ≥ 7) to explore the effect of fibromyalgic RA on treatment decisions. Chi-squared testing was then used to determine if there were differences between groups in treatment changes and also the kind of treatment change that was initiated.

To explore the effect of age on treatment decisions, patients were placed into three categories; under 45 years, 45-65 years and over 65 years. It also looked at the effect

of age of onset of RA on treatment decisions and patients were again placed into three categories depending on age at onset of disease; under 45 years, 45-65 years and over 65 years at onset of disease. Chi-squared testing was then used to determine if there were differences between groups in treatment changes and also the kind of treatment change that was initiated.

6.3. RESULTS

6.3.1. Temporal Changes Study

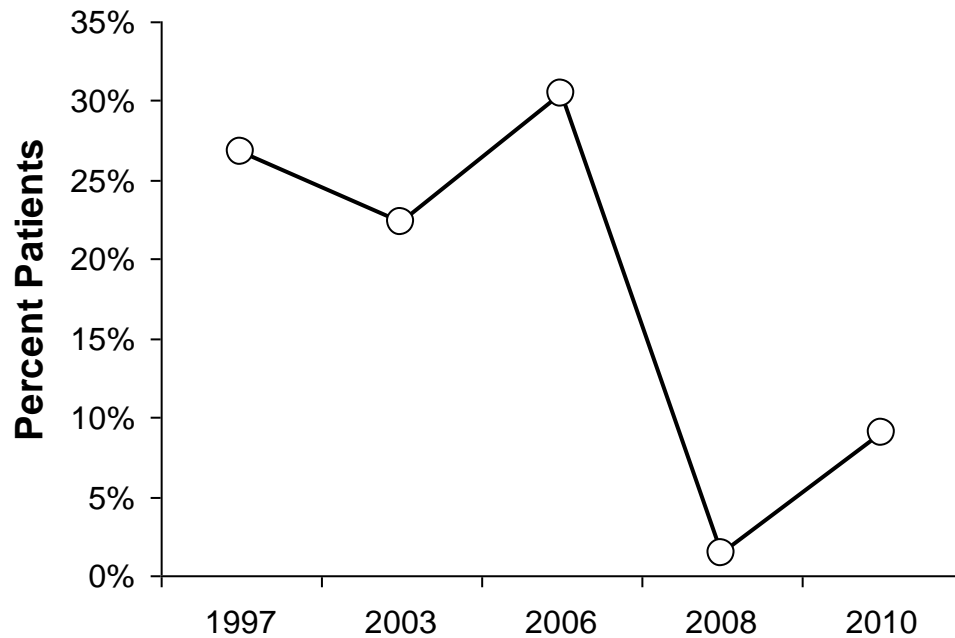
A total of 987 patients were included in the study. There were 202 patients from 1997, 300 patients from 2003, 105 patients from 2006, 71 patients from 2008 and 309 patients from 2010. Females predominated at 76% overall, this was similar in each year with 72% in 1997, 76% in 2003, 2006 and 2008 and 81% in 2010. Disease duration did not change significantly over time with an overall mean of 10.4 years (SD 10), with a range of 0 to 61 years. The mean disease duration in 1997 was 11 years (SD 10), in 2003 was 9 years (SD 10), in 2006 was 13 years (SD 11), in 2008 was 8 years (SD 8) and in 2010 was 11 years (SD10). The mean age overall was 59 years (range 18-89 years). In 1997 the mean age was 59 years (SD 13), in 2002 the mean age was 61 years (SD 13), in 2006 the mean age was 60 years (SD 14), in 2008 the mean age was 56 years (SD 15) and in 2010 the mean age was 59 years (SD 14).

Table 6:1 Patients Studied

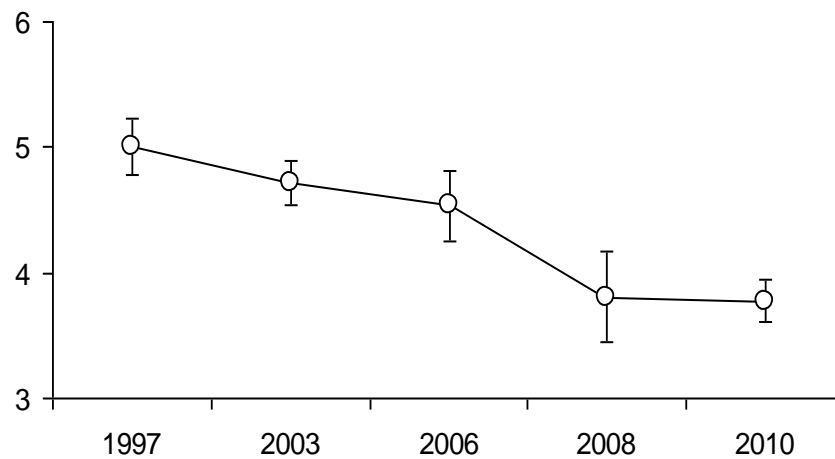
	Temporal Changes Study	Treatment Changes Study
<i>Disease Characteristics</i>	<i>Mean (Standard Deviation)</i>	
Disease Duration (years)	10.4 (10)	9.5 (9.0)
Tender Joint Count	6.6 (7.5)	4.4 (5.9)
Swollen Joint Count	4.4 (4.6)	3 (3.9)
Patient Global Assessment	45.7 (26.6)	38.2 (24.6)
ESR	30.5 (24.6)	29.4 (23.3)
DAS28	4.41 (1.63)	3.89 (1.50)
<i>Treatments</i>	<i>Percent</i>	
DMARDs	74	80
Biologics	10	16
Steroids	15	11

In total there were 182 patients (18%) who fit the criteria (≥ 7 tender minus swollen joints) for fibromyalgic RA. This number varies over time but overall seems to have reduced (27% in 1997 to 9% in 2010). (Figure 6.1)

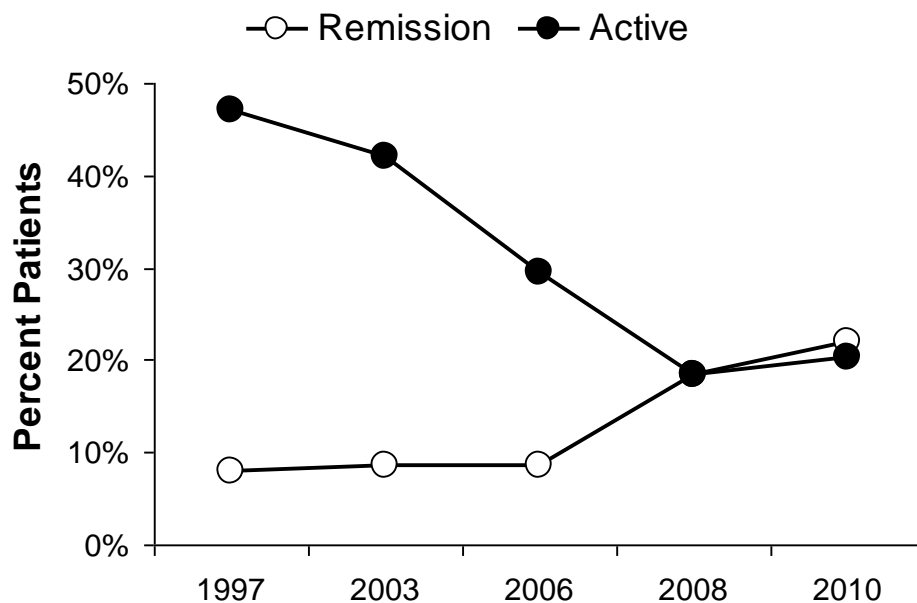
Figure 6:1 Fibromyalgic RA Over Time



The mean DAS28 overall was 4.41 (SD 1.63). The mean DAS28 score fell significantly over time; the mean DAS28 in 1997 was 5.01 (SD 1.64), in 2002 the mean DAS28 was 4.72 (SD 1.55), in 2006 the mean DAS28 was 4.53 (SD 1.44), in 2008 the mean DAS28 was 3.81 (SD 1.55) and in 2010 the mean DAS28 was 3.77 (SD 1.51). (Figure 6.2)

Figure 6:2 Changes in DAS28 Scores over Time

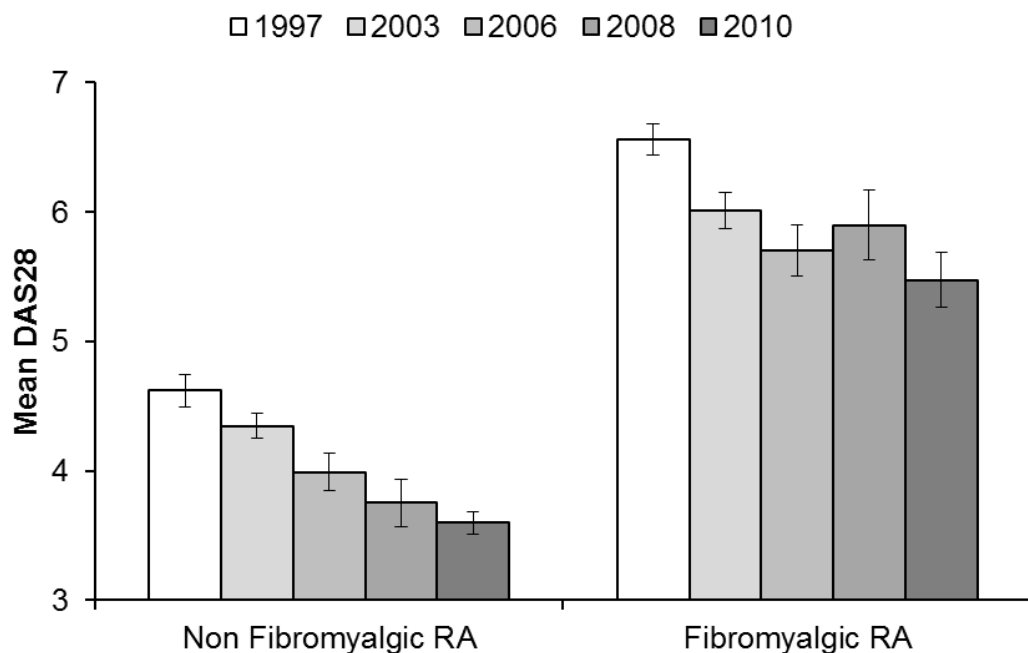
The number of patients classified as having high disease activity (DAS28 >5.1) also decreased over time (47% in 1997 to 20% in 2010), although this reduction seems to plateau after 2008. Equally the number of patients who achieved DAS28 remission (DAS28 <2.6) rose over the years (8% in 1997 to 22% in 2010), again a plateau effect is seen from 2008. (Figure 6.3)

Figure 6:3 DAS28 Remission and High Disease Activity over Time

Overall 11% of patients had fibromyalgic RA. Comparing mean DAS28 scores in fibromyalgic and non-fibromyalgic patients at each time point shows a gradual and

significant improvement over time in the non-fibromyalgic RA patients (4.62 (SD 1.50) in 1997 to 3.60 (SD 1.44) in 2010). However, fibromyalgic RA patients have mean DAS28 scores of over 5.1 at every time point measured with no sustained reduction in DAS28 over time. (6.56 (SD 0.92) in 1997 to 5.47 (SD1.13) in 2010). (Figure 6.4)

Figure 6:4 Fibromyalgic RA and DAS28 Over Time



The mean scores for tender joint counts and swollen joint counts, as well as patient global assessment and ESR were calculated for each year and showed a reduction in all constituents of the DAS28 over time, although there was less if any reduction in values between 2008 and 2010. The overall mean tender joint count was 6.6 (SD 7.5), falling from 9.9 (SD 9.4) in 1997 to 3.4 (SD 5.1) in 2008 and 4.0 (SD 5.5) in 2010. (Figure 6.5) The overall mean swollen joint count was 4.4 (SD 4.6), falling from 6.5 (SD 5.6) in 1997 to 2.9 (SD 4.2) in 2010. (Figure 6.6) Overall mean score for patient global assessment was 45.7 (SD 26.6), falling from 49.1 (SD 25) in 1997 to 39.7 (SD 25) in 2010. (Figure 6.7) The overall mean ESR was 30.5 (SD 24.6), falling from 35 (SD 26.2) in 1997 to 26.1 (SD 21.3) in 2010. (Figure 6.8)

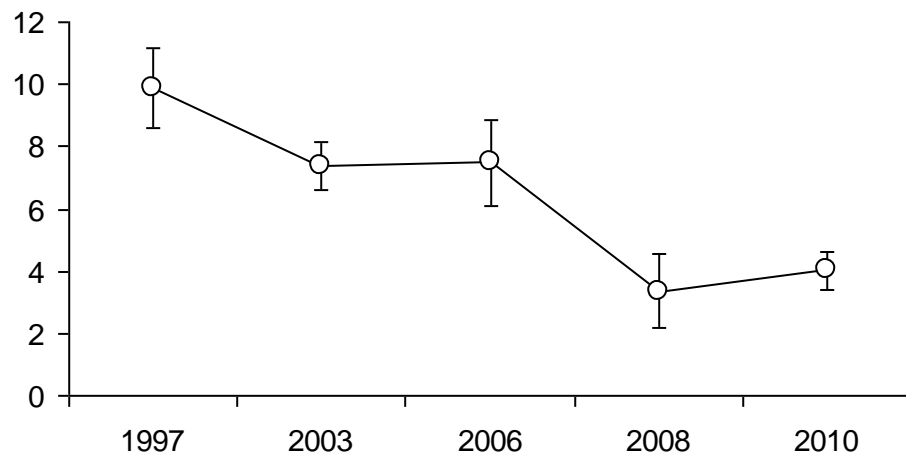
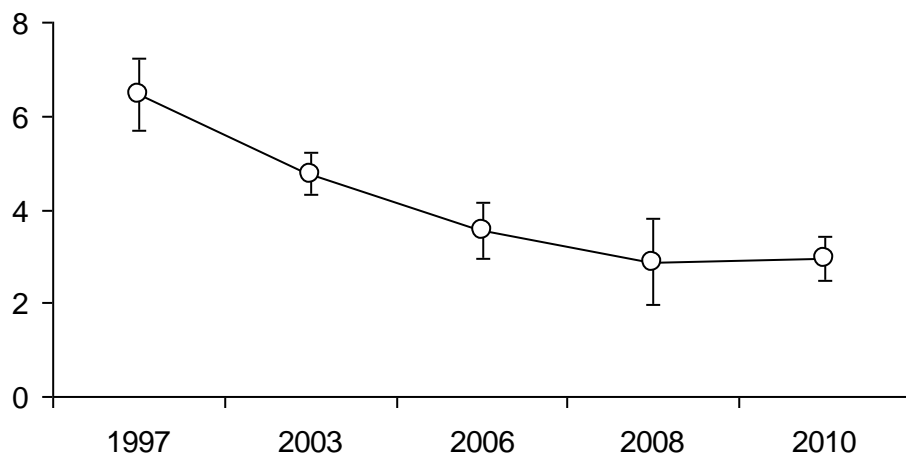
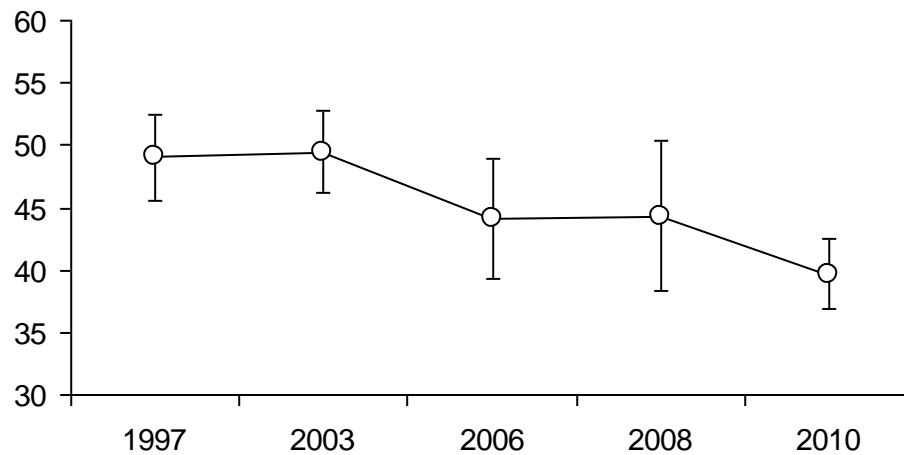
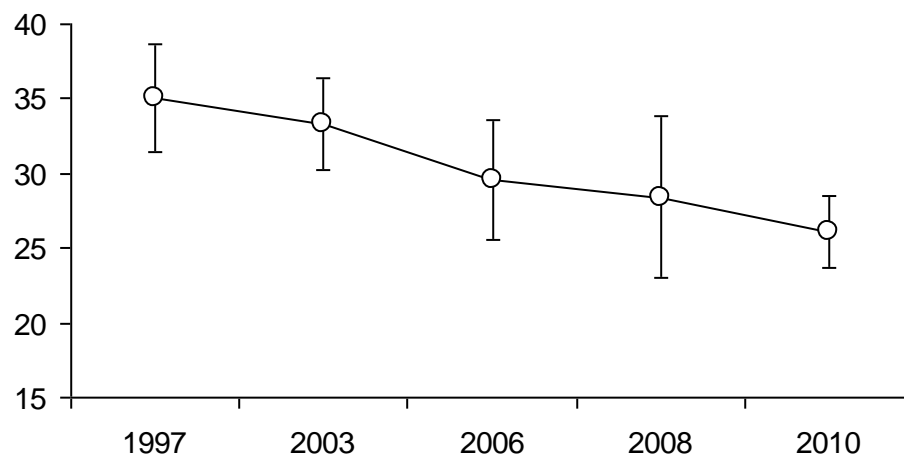
Figure 6:5 Changes in Tender Joint Counts over Time**Figure 6:6 Changes in Swollen Joint Counts over Time**

Figure 6:7 Changes in Patient Global Assessment over Time**Figure 6:8 Changes in ESR Over Time**

The number of patients taking NSAIDs has fallen over time, with an overall 40% of patients on NSAIDs; falling from 47% in 1997, increasing slightly in 2006 to 53% but falling to 26% in 2010. (Figure 6.9) The number of patients taking steroids increased from 11% in 1997 to 23% in 2002 but then fell over the next three time points to 10% in 2010. (Figure 6.10) There was an increase in the number of patients receiving DMARDs from only 58% in 1997, increasing to 86% in 2006 and then remaining stable at 80% in 2008 and 2010. (Figure 6.9) There was also an increase in the number of patients receiving combinations of DMARDs with only 1% of patients in 1997 receiving combination therapy, increasing to 21% in 2010. Likewise there

was an increase in the number of patients receiving biological therapy with no patients receiving biologics in 1997, increasing to 19% in 2006 and remaining stable at 18% and 17% in 2008 and 2010 respectively. (Figure 6.10)

Figure 6:9 NSAID And DMARD Use Over Time

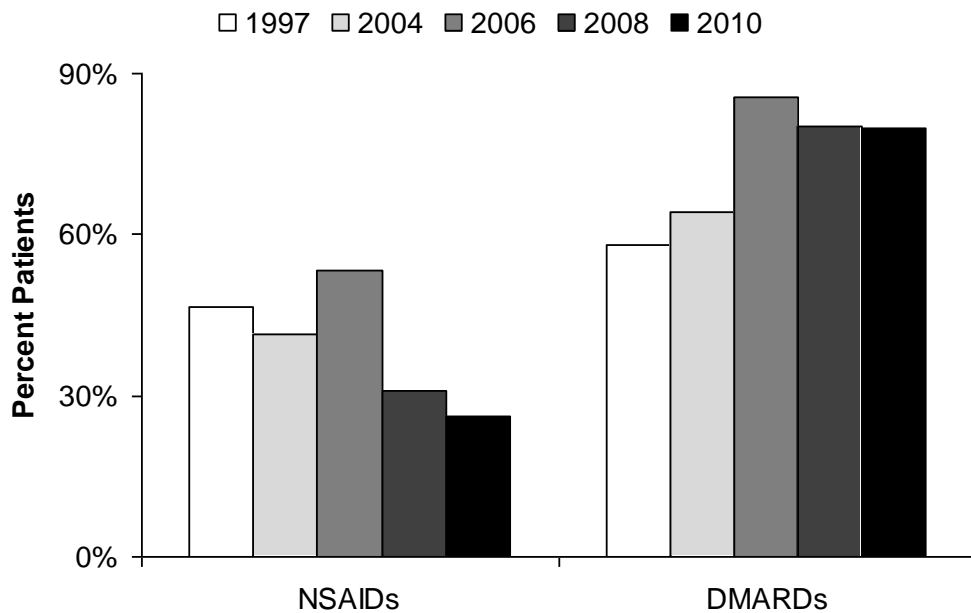
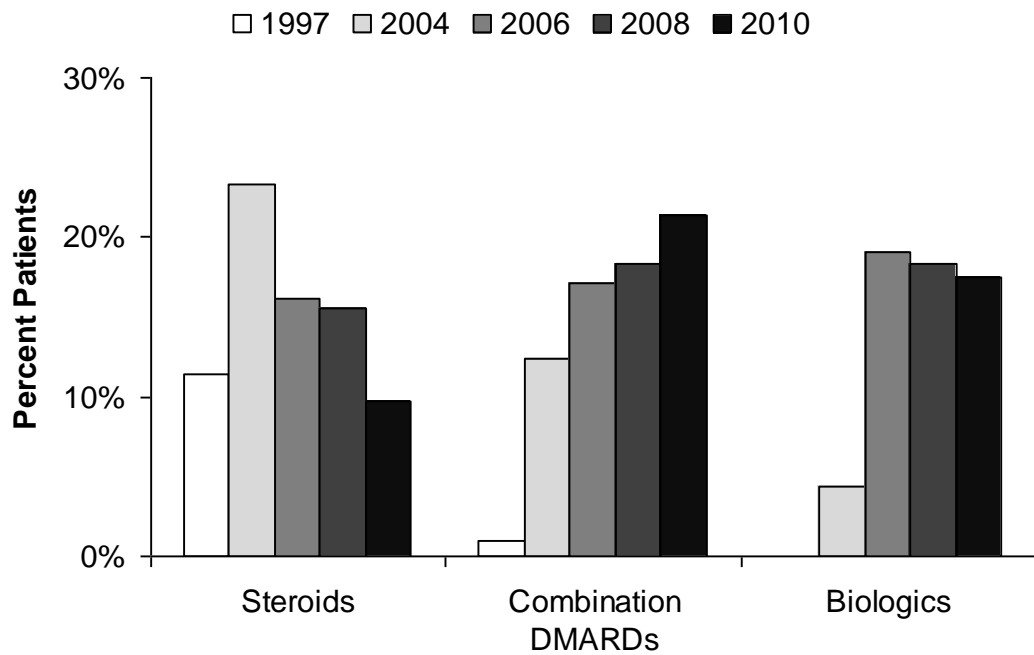


Figure 6:10 Other RA Treatments Over Time



6.3.2. Treatment Changes Study

A total of 482 patients from two sites were included in the study. The majority of patients were female (79%), 70% of patients were Caucasian, 19% of patients were of Black origin and 11% were from other ethnic backgrounds. The mean age was 59 years (range 24-89 years), with 38% of patients being over the age of 65 years, with a mean disease duration of 9.5 years (range 0-61 years), mean tender joint count of 4.4 (SD 5.9), mean swollen joint count of 3 (SD 3.9), mean patient global assessment of 38.2 (SD 24.6), mean ESR of 29.4 (SD 23.3) and a mean DAS28 of 3.89 (SD 1.50). Of the 482 patients, 80% were on a DMARD, 11% were on steroids and 16% were on biologic therapy (Table 6.1).

In total 34% of patients had a change to their treatment initiated at the clinic visit. The most common change in treatment was steroid (13%), 11% of patients had an increase in their current DMARD and 12% were given a new DMARD. The least common change was the initiation of a biologic therapy at 2.5%. Less than 1% of patients had a combination of changes to treatment; in every case this was the addition of steroid with a change to DMARD or biologic therapy.

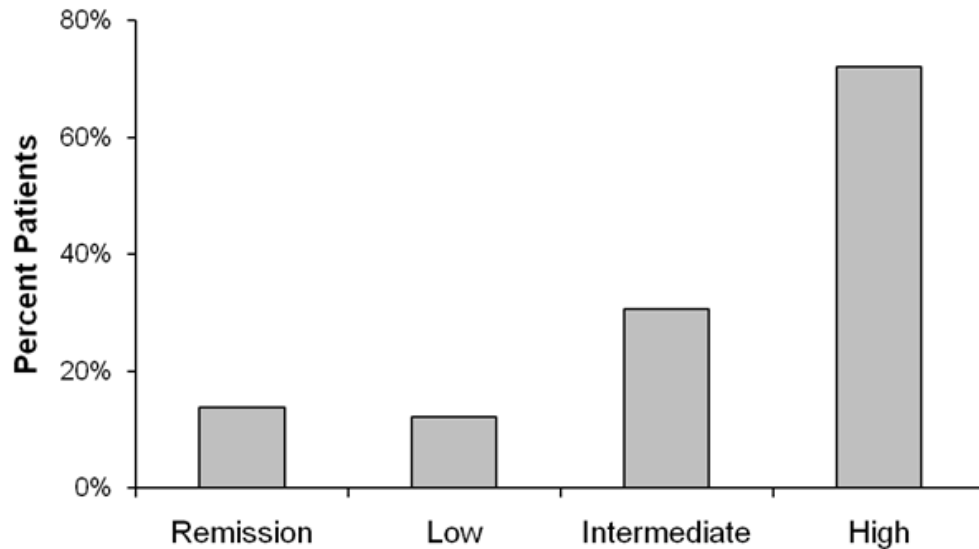
6.3.2.1. The Effect of DAS28 on Treatment Decisions

Twenty percent of patients were in remission according to DAS28 scores ($\text{DAS28} < 2.6$), 14% of patients were in the low disease activity category ($\text{DAS28} \geq 2.6$ to < 3.2), 45% of patients were in the intermediate disease activity group ($\text{DAS28} \geq 3.2$ to < 5.1) and 22% were in the high disease activity category ($\text{DAS28} \geq 5.1$). In those with DAS28 scores above 5.1, 24 patients had a DAS28 score of 5.1 to 5.5, 41 patients had a DAS28 score between 5.5 and 6.0, 13 patients had a DAS28 score between 6.0 and 6.5, 12 patients had a DAS28 score between 6.5 and 7.0 and 14 patients had a DAS28 score of over 7.0.

When comparing the number of changes within each DAS28 category most changes in treatment were seen in patients with high disease activity; 72% of these patients had a treatment change, meaning 28% had no treatment change despite DAS28 scores ≥ 5.1 . In contrast 86% of patients received no additional treatment if they were in remission according to DAS28 scores, which means that 14% of patients

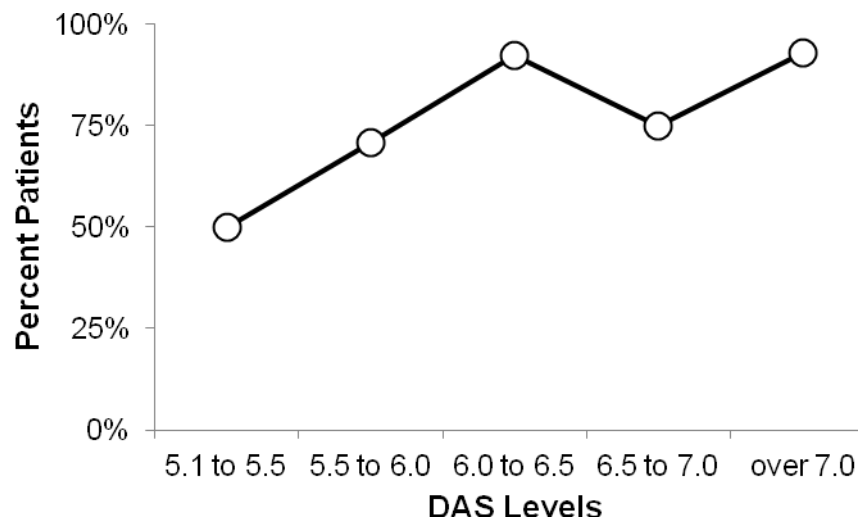
categorised as in remission received an escalation in treatment. Only 31% of patients with moderate disease activity in the intermediate group had a change in treatment and 12% of patients in the low disease activity group had a change in treatment. (Figure 6.11)

Figure 6:11 Treatment Changes and DAS28 Category



Looking at very active patients more closely, in those with DAS28 scores ≥ 5.1 , as the DAS28 score increases so does the likelihood of a change in treatment, ranging from a 50% chance of a change in treatment change if the DAS28 is between 5.1 and 5.5 to a 93% chance of a change in treatment if the DAS28 score is over 7.0. (Figure 6.12)

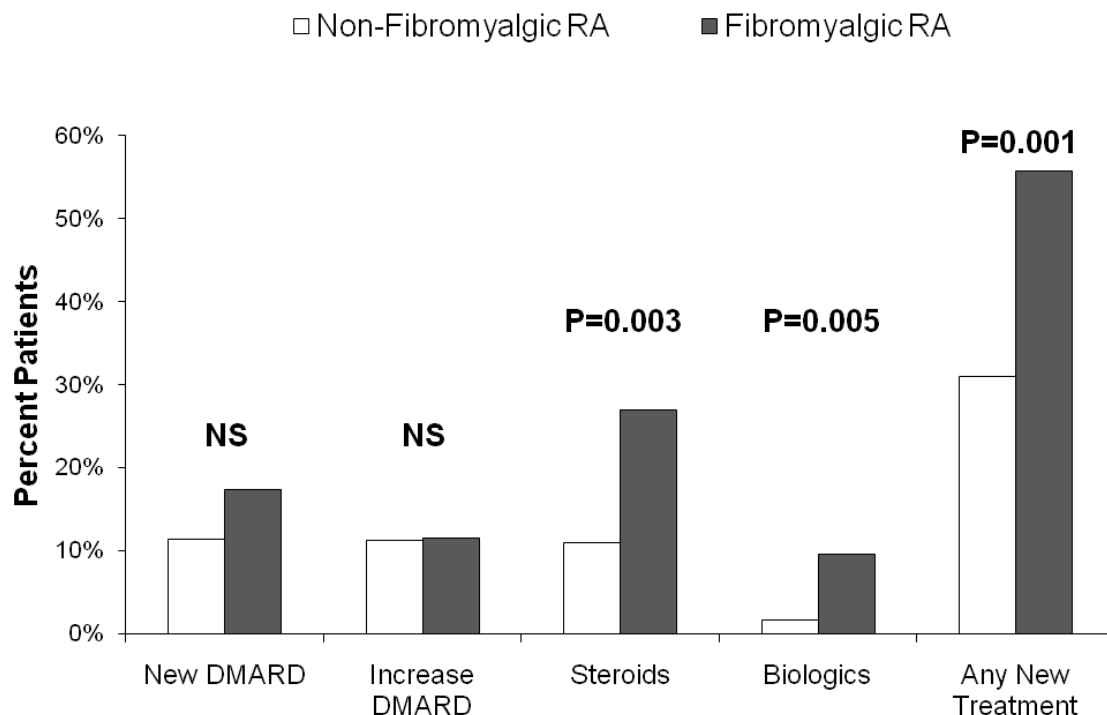
The changes for each disease activity category, according to the type of treatment change is summarised in Table 6.2. This showed that the most common treatment change in patients with high disease activity was the addition of steroids (35%) and the most common change of treatment for those in the remission and low disease categories was an increase in DMARD (11% and 6%, respectively), for those in the intermediate disease activity group the most common change to treatment was the addition of a new DMARD.

Figure 6:12 Treatment Changes In Patients with High Disease Activity**Table 6:2 Treatment Changes and DAS28 Categories**

DAS Categories	Remission	Low	Intermediate	High
<i>No change</i>	86%	88%	69%	28%
<i>Increase DMARD</i>	11%	6%	11%	15%
<i>New DMARD</i>	3%	5%	12%	26%
<i>Oral/IM Steroids</i>	2%	2%	10%	35%
<i>Biologics</i>	0%	0%	1%	10%

6.3.2.2. The Effect of Fibromyalgic RA on Treatment Changes

Patients with fibromyalgic RA had significantly higher DAS28 scores than non-fibromyalgic RA (5.54 (SD 1.12) vs. 3.68 (SD 1.41) $p=0.04$). Fibromyalgic RA patients also had a significantly higher chance of having a treatment change overall (56% fibromyalgic RA vs. 31% non-fibromyalgic RA, $p=0.001$). This trend was not seen across all types of treatment change. There was no significant difference in the chance of being prescribed a new DMARD or having your current DMARD increased in dose whether patients did or did not have fibromyalgic RA. However, if patients had fibromyalgic RA they were more likely to be given steroids (27% fibromyalgic RA vs. 11% non-fibromyalgic RA, $p=0.003$) or biologics (10% fibromyalgic RA vs. 2% non-fibromyalgic RA, $p=0.005$). (Figure 6.13)

Figure 6:13 Fibromyalgic RA and Treatment Changes

6.3.2.3. What Influences Changes in Treatment?

Univariate Analysis

Univariate analysis using odds ratios, showed significant associations between the chance of a change in treatment and age (0.98, $p=0.003$), ethnicity (1.34, $p=0.035$), DAS28 (2.25, $p<0.001$), fibromyalgic RA (2.81, $p=0.001$) and being on a biologic therapy (0.58 $p=0.05$). Disease duration only just failed to gain significance at the 0.05 level (0.98, $p=0.07$). No association was found between change in treatment and gender, current DMARD or steroid use. (Table 6.3) There were also significant associations between the chance of having a treatment change and each component of the DAS28 when they were substituted instead of the DAS28: Tender joint count 1.16 $p<0.001$, swollen joint count 1.31 $p<0.001$, ESR 1.03 $p<0.001$ and patient global assessment 1.03 $p<0.001$.

Multivariate Analysis

Multivariate analysis was then used to determine the most important factors influencing treatment change in RA. Those variables which had significance at the

univariate level were included in the multivariate level and disease duration was also included in the final model. In the first model DAS28 was used as the measure of disease activity. This showed that only two factors retained significance at the multivariate level; age (odds ratio 0.97, $p=0.002$) and DAS28 (odds ratio 2.45, $p<0.001$). Ethnicity, disease duration, fibromyalgic RA and current biologic therapy showed no significant association in the multivariate analysis. (Table 6.3)

In the second model the components of the DAS28 were included which all had significance at the univariate level and excluded DAS28. This showed again that age retained significance (odds ratio 0.97, $p=0.003$), of the components of the DAS28 the only component which did not retain significance in the multivariate analysis was tender joint count. Swollen joint count had an odds ratio of 1.18 ($p<0.001$), ESR 1.02 ($p<0.001$) and patient global assessment 1.02 ($p=0.002$). As in the first model ethnicity, disease duration, fibromyalgic RA and current biologic therapy showed no significant association in the multivariate analysis. (Table 6.4)

Table 6:3 Factors Influencing Treatment Changes with DAS28

	Univariate		Multivariate	
	<i>Odds Ratio (95%CI)</i>	<i>Signif</i>	<i>Odds Ratio (95%CI)</i>	<i>Signif</i>
Age	0.98 (0.97, 0.99)	0.003	0.97 (0.96, 0.99)	0.002
Gender	1.06 (0.67, 1.68)	NS	-	-
Ethnicity	1.34 (1.02, 1.75)	0.035	0.87 (0.63, 1.25)	NS
Disease Duration	0.98 (0.96, 1.00)	0.07	0.98 (0.96, 1.01)	NS
DAS28	2.25 (1.90, 2.68)	<0.001	2.45 (2.00, 3.00)	<0.001
Fibromyalgic RA	2.81 (1.57, 5.01)	0.001	0.72 (0.35, 1.48)	NS
Biologics	0.58 (0.33, 1.00)	0.05	0.55 (0.29, 1.06)	NS
DMARD	0.86 (0.54, 1.36)	NS	-	-
Oral Steroids	0.90 (0.49, 1.62)	NS	-	-

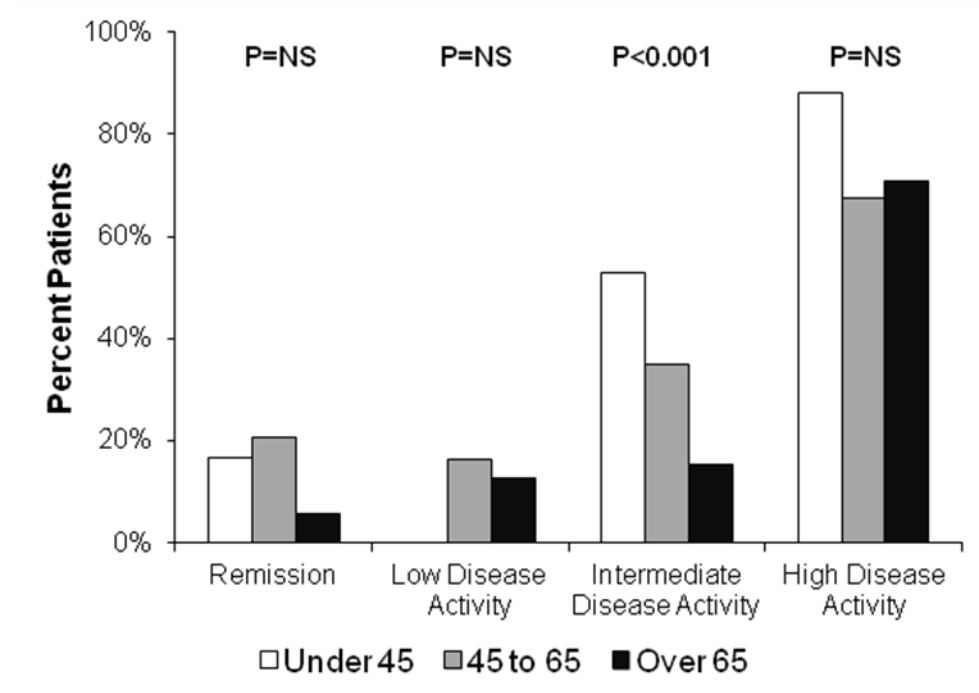
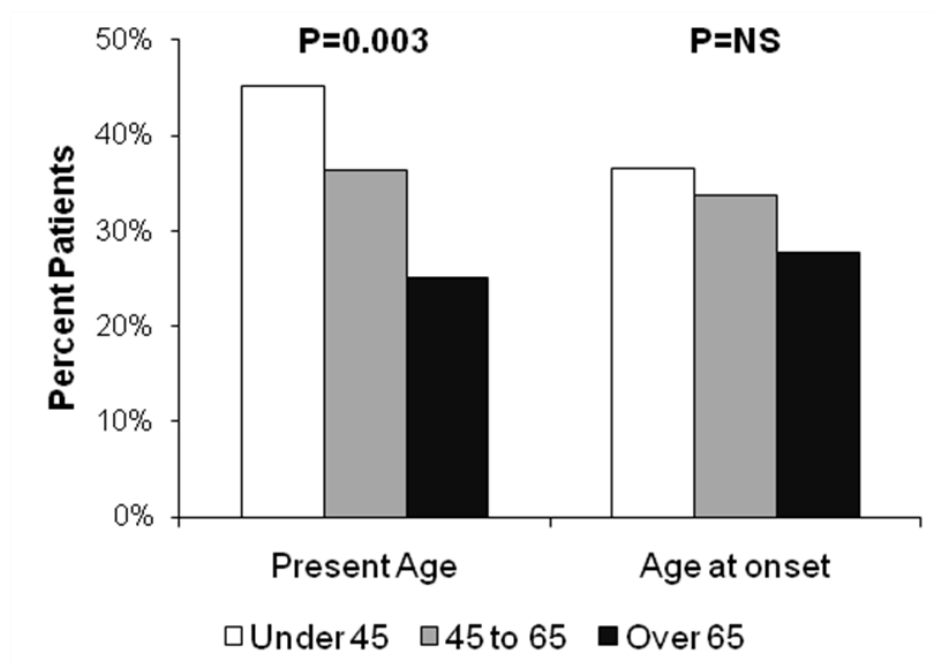
Table 6:4 Factors Influencing Treatment Changes with DAS28 Components

	Univariate		Multivariate	
	<i>Odds Ratio (95%CI)</i>	<i>Signif</i>	<i>Odds Ratio (95%CI)</i>	<i>Signif</i>
Age	0.98 (0.97, 0.99)	0.003	0.97 (0.96, 0.99)	0.003
Gender	1.06 (0.67, 1.68)	NS	-	-
Ethnicity	1.34 (1.02, 1.75)	0.035	0.93 (0.6, 1.32)	NS
Disease Duration	0.98 (0.96, 1.00)	0.07	0.99 (0.96, 1.01)	NS
Tender Joint Count	1.16 (1.12, 1.21)	<0.001	1.07 (0.99, 1.15)	NS
Swollen Joint Count	1.31 (1.22, 1.41)	<0.001	1.18 (1.10, 1.29)	<0.001
ESR	1.03 (1.02, 1.04)	<0.001	1.02 (1.01, 1.03)	<0.001
Patient Global	1.03 (1.02, 1.04)	<0.001	1.02 (1.01, 1.03)	0.002
Fibromyalgic RA	2.81 (1.57, 5.01)	0.001	0.96 (0.32, 2.88)	NS
Biologics	0.58 (0.33, 1.00)	0.05	0.61 (0.31, 1.19)	NS
DMARD	0.86 (0.54, 1.36)	NS	-	-
Oral Steroids	0.90 (0.49, 1.62)	NS	-	-

6.3.2.4. The Effect of Age on Treatment Decisions

As age was shown to be important in treatment decisions using a multivariate model this variable was looked at more closely. Patients were divided into three groups according to age; under 45 years (17%), 45 to 65 years (45%), and over 65 years (38%). The relationship of treatment change with age of onset of disease was explored. Patients were grouped into the same three categories; under 45 years at onset of disease (39%), 45-65 years at onset of disease (42%) and over the age of 65 years at onset of disease (16%).

The different age groups were applied to each DAS28 category and chi-squared testing showed that there were no significant differences in treatment changes between age groups in the remission, low disease activity and high disease activity categories. However, age had a significant impact on the chance of having a treatment change in those patients with moderate disease activity in the intermediate group (53% in patients under 45 years, 35% in patients 45-65 years and 15% in patients over 65 years, $p < 0.001$). (Figure 6.14)

Figure 6:14 Treatment Changes, DAS28 Categories and Age**Figure 6:15 Treatment Changes, Current Age and Age at RA Onset**

Although there was a significant difference in treatment changes overall depending on current age (under 45 years 45%, 45-65 years 36%, over 65 years 25%, $p=0.003$),

there was no significance in changes to treatments with age at onset of disease. (Figure 6.15)

There was also no significant difference in the use of steroids or DMARDs between age groups or in age at onset. (Figures 6.16 and 6.17) There was however, a significant difference in the use of biologics, with no difference seen with current age but a reduced number of patients who developed RA when they were over the age of 65 years receiving biological therapy. Of the patients who were under the age of 45 years at onset of disease, 22% of patients were given biological therapy, 16% of patients who developed RA between the ages of 45 and 65 years, and only 7% of patients who developed RA after the age of 65 years were given biological therapy ($p=0.012$). (Figure 6.18)

Figure 6:16 DMARD Use, Current Age and Age at RA Onset

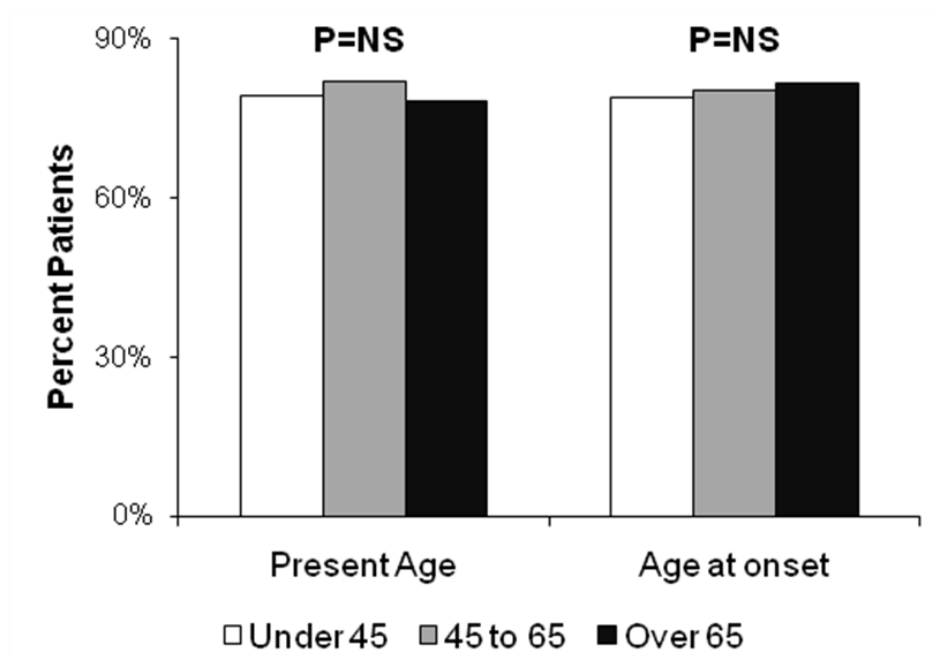
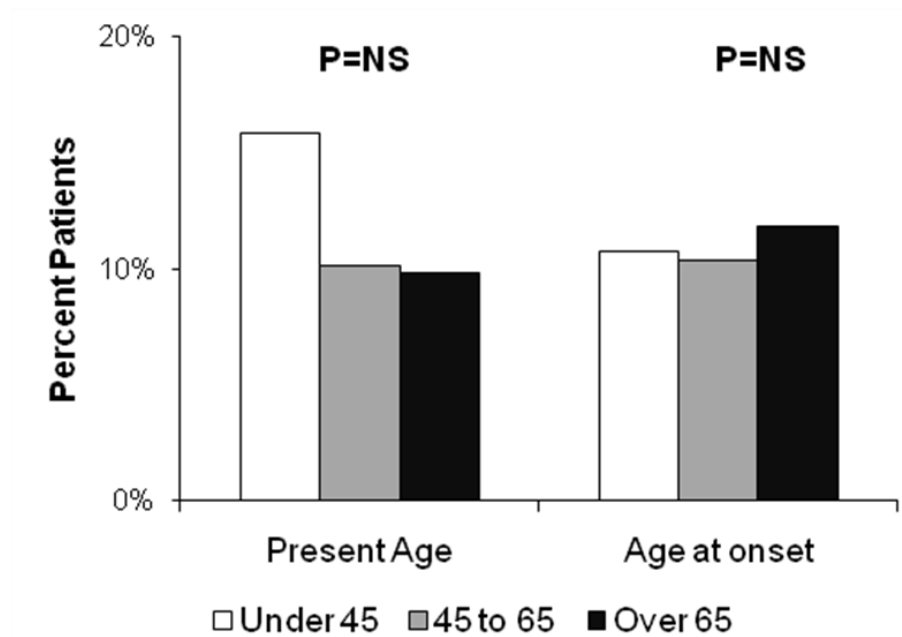
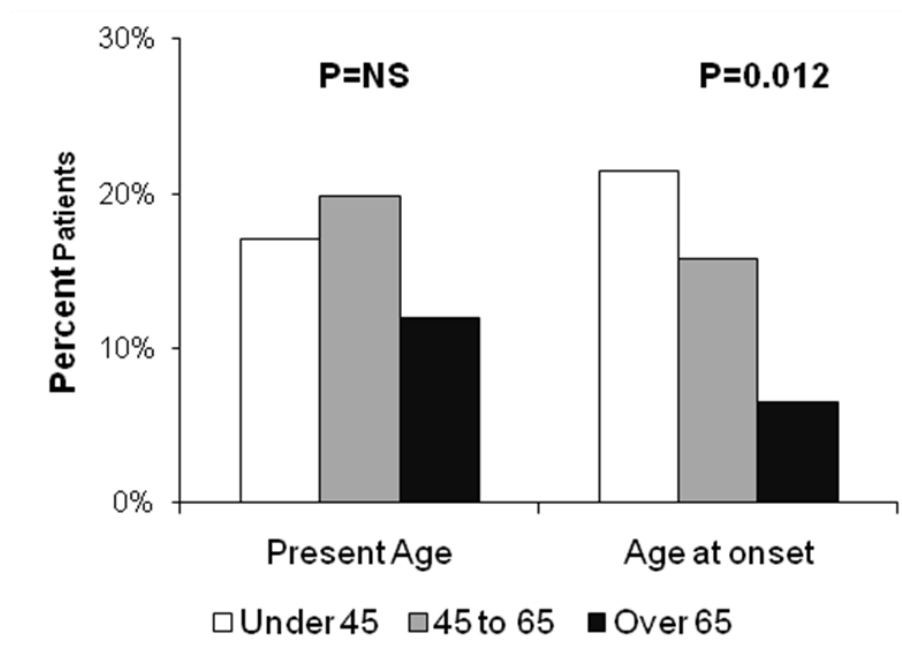


Figure 6:17 Steroid Use, Current Age and Age at RA Onset**Figure 6:18 Biologic Use, Current Age and Age at RA Onset**

6.4. DISCUSSION

6.4.1. Temporal Changes Study

The study showed that the DAS28 has fallen significantly over the years from a mean of 5.01 in 1997 to a mean of 3.77 in 2010. The fall in DAS28 however, does seem to have plateaued over the last few years. There was gradual reduction in DAS28 until 2008, with no significant fall between 2008 and 2010. The individual components of the DAS28 also saw significant reductions over time but again most plateaued from 2006 (swollen joint count, patient global assessment) or 2008 (tender joint count, ESR) onwards. These improvements in DAS28 could be explained by the change in treatment strategies which have been advocated in the last few years. The focus of treatment has very much shifted to treating early and attaining tight control of disease. [NICE CG79 2009] Why improvements in disease activity seem to have plateaued over the last few years is not clear.

The prevalence of fibromyalgic RA does seem to have decreased over time and whether this reflects the effects of better treatment is unclear. Those patients with fibromyalgic RA continue to have high DAS28 scores which have not changed over time, as opposed to non-fibromyalgic RA patients who showed a gradual and significant reduction in DAS28 over time. This would suggest that for these patients other treatment strategies are needed other than just targeting disease activity as their DAS28 scores may be falsely elevated by a large contribution from patient global assessment and tender joint counts.

The improvements in DAS28 are mirrored by the increase in the use of combination therapies with a large increase seen between the 1997 and the subsequent cohorts. There was a non-sustained increase in the use of steroids between 1997 and 2003. This in part may be explained by publications of studies around this time influencing prescribing practice. Kirwan et al published data on the effect of low dose prednisolone in RA in 1995 and then the COBRA study which looked at combinations of prednisolone with DMARDs versus monotherapy in early RA was published in August 1997 [Boers et al. 1997]. Further influential studies were published in 2004 and 2005 which may have changed prescribing habits as both

came out in favour of combination therapies; the TICORA (Tight Control for RA) study [Grigor et al. 2004] and the BeSt study [Goekoop-Ruiterman et al. 2005].

The only drugs which saw a reduction over time were non steroidal anti-inflammatories. There are likely to be two main reasons for the decline in use of NSAIDs; the withdrawal of rofecoxib in 2004 saw a decline in prescription because of the concern of the increase in cardiovascular risk with the use of rofecoxib and whether it was a class effect. Secondly there has been a lot of work looking at cardiovascular risk in RA in the last few years with a particular focus on NSAIDs [Scott et al. 2007] and the prescription of NSAIDs seems to have fallen even further.

The study also showed an increase in biologic use since 2003, which would fit with the approval and guidance from NICE (National Institute for Health and Clinical Excellence) in 2002 [NICE TA36]. Again the use of biologics has not changed significantly since 2006. The plateau in use of biologics in the cohorts may reflect the fact that, although more treatments are available for RA, these drugs remain expensive and are currently only used under guidance from NICE in the UK and in the current economic climate there is likely to be pressure on the prescription of these expensive drugs. It is therefore important to focus more closely on the use of combination therapies and although the number of patients having combination DMARDs has increased over time there were still only 21% of patients receiving this type of treatment. This number of patients on combination DMARDs was similar to those seen in the ERAN cohort who reported 26% of patients on combination therapy [Kiely et al. 2010] and slightly higher than the 15.6% on multiple DMARDs seen between 2005 and 2007 in a Canadian cohort [Tavares et al. 2011]. There are current studies underway looking at the efficacy of combination therapy versus biologic therapy which may have important economical impacts.

6.4.2. Treatment Changes Study

The previous study showed that disease activity scores have improved significantly over the last 15 years. However, there are still a significant number of patients with active disease as defined by the DAS28. Only 20% of patients in this study of 482 RA patients were classified as being in remission (DAS28<2.6). Overall however,

only 34% of patients had a change in treatment, although the higher the DAS28 the more likely a patient was to have a change in treatment. Those patients with high disease activity ($\text{DAS28} \geq 5.1$) had their treatment changed 72% of the time. Those patients with even higher DAS28 scores were more likely to have a change in treatment and the chance of having a treatment change approaches 100% when the DAS28 is over 7.0. This still means that there are a considerable number of patients not having an increase in treatment despite having high disease activity. Perhaps more concerning is the lack of treatment change in those patients with moderate/intermediate disease activity. Only 31% of patients with moderate disease had a change in treatment.

There may be several reasons behind this apparent lack of treatment changes, including patient choice, concomitant disease limiting DMARD use or intolerance to DMARDs. The effect of fibromyalgic RA is slightly more complex. The results show that if a patient has fibromyalgic RA there is a greater chance overall of having a change in treatment, although this effect is only seen with changes in treatments involving steroids and biologics. The fibromyalgic RA patients had higher DAS28 scores compared to non-fibromyalgic RA and the increased chance of having a change in treatment may be explained by this observation. The fibromyalgic RA patients had a mean DAS28 of 5.54, putting them in the high disease activity category and this also may mean they are eligible for biologic therapy. If treatment changes are led only by DAS28 then it would not be surprising to see an increase in the number of fibromyalgic patients given biologics. Some clinicians however, may use clinical judgment rather than DAS28 to solely determine treatment changes and may explain why some patients with apparent active disease do not have their treatment changed.

The DAS28 did have a strong influence on treatment decisions in this cohort and treatment decisions are swayed more by objective signs of inflammation (swollen joint count and ESR) and also patient global assessment but not by tender joint counts. The multivariate analysis showed that age has an effect on treatment decisions and retained significance in the multivariate analysis. This suggests that the older you are the less likely you are to have change in treatment. The effect of age on whether you have a change in treatment is most apparent in the intermediate

category, with no apparent differences seen in the remission and low disease activity categories and no difference once you develop a high disease activity state. The possible reasons for this may be that clinicians are willing to accept a degree of disease activity in the older population, as they feel that the burden of disease progression and disability will be less than a younger patient who is likely to have a longer life span. Older patients are likely to have more co-morbidities than younger counterparts, and this may influence our treatment decisions although if this is the case clinicians do not seem to be concerned about this when disease activity becomes high as there is no difference in treatment changes with age for this category. These possible reasons may explain the other observation that if you develop RA after the age of 65 years you are less likely to be given a biologic therapy although there is no difference in the prescription of DMARDs or steroids. One final reason which may explain this phenomenon is patient choice which was not explored in this study.

CHAPTER 7. DISCUSSION

7.1. SUMMARY OF FINDINGS

7.1.1. Key Issues

The conclusions in this thesis are based on data collected predominantly in South East London and must be assessed within this context; as organisation of provision of care can vary within different parts of the UK. The results in this thesis also clearly reflect an inner city population which has a diverse ethnic mix. The ethnic mix seen within South East London means a higher number of patients with Afro-Caribbean and Asian backgrounds were represented and therefore the findings may not be generalisable to the rest of the UK. However, similar findings have been found in other parts of the UK and are discussed in detail below. Despite these caveats the research in this thesis has identified a number of limitations to care, which are particularly important in relation to the provision of high quality care for patients with RA. These fall into three broad areas, as follows:

Firstly, it showed that current care is not optimal. Particular problems care included the following:

- It is not sufficiently patient centred
- Management is not integrated across the primary/secondary care divide
- The focus of care over-emphasises drug treatment and overlooks care of the whole person.

Secondly, care does not deal with a number of crucially important areas to patients with RA. These include the following:

- Fatigue, which is a key problem for patients, receives little attention
- Pain, which is a dominant symptom of RA, is often not directly addressed
- Patients with the fibromyalgic rheumatoid clinical phenotype do not receive treatment that is specifically tailored to their needs.

Finally, by using patient-centred outcomes treatment decisions will be improved as follows:

- There should be a greater understanding of the need to increase adherence with treatment
- The potential for treatment decisions to be influenced by age will be identified

- The delivery of targeted treatments involving patients' views will be attainable.

Looking at these three broad areas it is clear that with regard to patients concerns two main themes emerge. Firstly, many patients concerns are related predominantly to environment, society and care delivery. These findings will be influenced by the organisation of medical provision within the institution in which the research was conducted. Secondly, the symptomatic concerns of pain and fatigue and the psychological impacts may be inherent to the disease process but the expression of these symptoms may have a cultural setting as ethnicity has been found to be a predictor of depression in RA [Margaretten et al. 2009] and therefore the findings in our ethnically diverse population need to be considered. Although pain is a symptom that is common in RA and accompanies active disease; chronic pain and fatigue as well as psychological distress are symptoms that are often seen in other chronic diseases such as chronic obstructive pulmonary disease, multiple sclerosis and diabetes [Bentsen et al. 2013; Yamout et al. 2013; Flachenecker et al. 2002; Sudore et al. 2012] and as such these findings may not be disease specific but may reflect in part the consequence of chronic disease.

The issues raised by these studies are considered in more detail in the subsequent sections.

7.1.2. Current Care

7.1.2.1. Standards of Care

The standards of care audit shows many areas need to be improved before care meets the ARMA standards. Those areas in which there is room for improvement include giving information, providing written care plans and giving advice about exercise programmes. In patients with a new diagnosis of RA only a third had seen a physiotherapist, less than 10% had seen an occupational therapist and no-one had seen a podiatrist within six months of diagnosis. Co-morbidities are also not being routinely checked including blood pressure and cholesterol assessments; both these need to be addressed to deal with the increased risk of heart disease in RA patients.

Despite relative shortfalls in the service provided, patients are satisfied with the care they receive, with an overall satisfaction rate of 3.89. Technical quality scored highest. As there were low empathy scores it is likely there is some way to go in addressing patients' concerns.

7.1.2.2. Patients Needs

The qualitative study identified three key areas of importance to RA patients: the personal impact of RA, information needs and health care delivery. Although most RA patients receive some written information about their disease, many wanted to know more about RA and its treatment. Further information is needed about the disease, its treatment and services and benefits available at both a national and local level.

Most rheumatologists agree RA patients should have immediate access to specialist advice when their RA is flaring. Patients have the same view but have commented on the difficulty in achieving it. Some patients use the relationship they have developed with specialist nurses to gain access to rheumatologists in times of need whereas as a considerable number of patients will just 'grin and bear it'. Continuity of care is important for patients as is being given time in an appointment and having an understanding and sympathetic attitude. Patients dislike waiting for long periods to be seen and then for the appointment to be rushed. These considerations need to be taken into account when designing follow up clinics for RA patients, this will not necessarily be easy given the pressures on appointments but ensuring that patients are seen by both specialist nurse and doctors appears essential.

7.1.2.3. Barriers to Integrated Care

The qualitative study identified three areas in which there were perceived barriers to seamless integrated care in RA from the perspective of patients, carers, specialists and GPs. These are early referral, limitations of ongoing care for established RA and management of acute flares. The study took place when NICE guidelines and other UK care strategies were being developed; these help place the findings in context. These themes could either be general ones or represent local issues which are not generalisable. It is impractical to provide an answer from a single centre study and

national audits are needed to find out; there are moves to start these in the near future.

Delay in referral, highlighted in the present study, has also been suggested in previous guidelines and UK observational studies [National Audit Office; King's Fund]. The Norfolk Arthritis Register [Harrison et al. 2000] and the Steroids in Very Early Arthritis trial [Verstappen et al. 2010] have shown it is possible to see patients with inflammatory arthritis in the early stages of their disease. Delay in referral reflects several complex factors including both organisational issues and patient issues. There may be disparities between observed and perceived time to referral in patients with long disease durations who find it difficult to accurately estimate delays retrospectively. Patients may also take time to identify their symptoms and hence achieve referral, which may be reflected in a perceived delay in referral. One clear message from research with GPs was their concerns about their role as "gatekeepers" to secondary care. This potentially creates reluctance to refer patients with possible inflammatory arthritis, which can create a barrier to seeking specialist advice which needs to be removed.

Several limitations in the management of established RA could be overcome by changes in the arrangements of the service. One issue is insufficient time in secondary care appointments so that clinicians do not fully address major concerns for patients. Greater involvement of specialist nurses has been helpful [Tijhuis et al. 2003], but is not enough by itself. Specialists need to devote more time and resources to the follow up of patients with established RA [Lempp et al. 2006]. The NHS Musculoskeletal Framework may help by transferring stable musculoskeletal disorders to community based units and allowing specialists to focus on managing RA. This will require a re-evaluation of new to follow-up ratios as low ratios, often considered a mark of effective care, may indicate poor quality care in RA.

Another issue is the limited knowledge many GPs have about RA [Stewart et al. 2009; Bernatsky et al. 2010; Jacobi et al. 2004]. This reflects the absence of musculoskeletal disorders from the Quality and Outcomes Framework and the dearth of rheumatology teaching in the postgraduate training of UK GPs [National Audit Office 2009]. It is impractical to equip all GPs with enough expertise to make

significant inputs into the management of RA patients; the best solution may be to make better use of those GPs with expertise in the field.

A final issue is the need for close collaboration between primary and secondary care. As RA is relatively uncommon, GPs have limited knowledge about the disease; much of its care needs to be managed by specialists. There also need to be better links between specialists and the community they serve. The best way to achieve this goal will need to be determined locally as it will depend on issues like travel for patients and local community facilities.

Although we have discussed the barriers to care within our local area and how these might be addressed new guidelines have subsequently been produced by NICE regarding management of RA. [NICE Clinical Guideline 79, 2009] Patient centred care is an essential part of the guidelines and they have set out what they feel is best patient care for RA patients and should be achievable on a national level. From our study it is clear that not all standards are being met at least within this population, particularly with reference to monitoring, review and access to a multidisciplinary team. As new guidance is issued such as the Best Practice Tariff for early inflammatory arthritis where financial incentives are given to provide best quality care; [Department of Health 2012] it will be important for rheumatologists to assess their services to ensure that best care is provided as set out by national organisations such as NICE.

7.1.3. Patient Centred Outcomes

7.1.3.1. Fatigue and Its Clinical Associations

Fatigue is a dominant symptom in RA. In keeping with previous reports [Huyser et al. 1998; Riemsma et al. 1998; Rupp et al. 2004; Tack 1990; Fifield et al. 1998; Wolfe et al. 2004; Suurmeijer et al. 2001; Fifield et al. 2001; Crosby 1991; Jump et al. 2004] the studies in this thesis show it is strongly associated with pain. Patients with active RA had high levels of fatigue; however regression analysis showed this relationship was less important than the association with pain. Patients diagnosed with either fibromyalgia and/or depression also had higher levels of fatigue. As these

conditions co-aggregate, after appropriate adjustment, depression was the only co-morbidity invariably associated with fatigue. Fatigue was also influenced by disability; HAQ scores were positively associated, suggesting patients with high fatigue levels are more disabled.

If fatigue is widely adopted as an RA outcome measure, it is crucial to identify the best instrument to assess it. Although VAS fatigue scores are simple and reproducible, multidimensional assessments provide a more complete picture and improve our understanding of the clinical relationships of fatigue. Validated instruments that measure RA fatigue like the Multidimensional Assessment of Fatigue (MAF) [Belza et al. 1993] and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [Cella et al. 2005] may prove valuable, especially in assessing the mechanism of fatigue.

7.1.3.2. Treatment and Fatigue

RCTs show adalimumab [Weinblatt et al. 2003] methotrexate and leflunomide [Strand et al. 2005] reduce fatigue. These falls in fatigue are accompanied by decreases in disease activity. Observational studies in established disease show that in routine practice, fatigue decreases when active RA is treated with anti-TNF and to a lesser extent with DMARDs. These falls mirror decreases in DAS scores and pain. TNF receptors have been identified on neurons [Pollock et al. 2002] and chronic inflammation is associated with upregulation of these TNF receptors [Inglis et al. 2005]. TNF has also been implicated in pain pathways [Empl et al. 2001] and thus in conditions such as RA the increase in TNF levels may contribute to chronic inflammatory pain. The improvement in pain and fatigue with anti-TNF therapy may be due to a direct central effect through interaction with sensory neurons.

The early RA study highlights the impact of early RA across most aspects of health. The SF-36 showed substantial overall reductions in quality of life, compared to normal populations [Garratt et al. 2003]. Although treatment over twelve months showed improvements in the physical domains of the SF-36 (physical function and role physical) there were no significant changes in vitality, social function and mental health domains. This would suggest that a broader range of treatment

approaches would benefit early RA patients, focusing on mental as well as physical health.

7.1.3.3. Fatigue and Disability

RA disability is influenced by disease activity, joint damage, co morbidities, psychosocial factors and depression [Pollard et al. 2006; Esclante et al. 1999; Sokka et al. 2000; Wolfe 2000; Rupp et al. 2006; Gettings et al. 2010; Hazes et al. 2010]. Many of these factors have cultural contexts [Ravindran et al. 2008; Griffiths et al. 2000; Bruce et al. 2007]. Our results confirm fatigue is another important driver of RA disability. The relationship between fatigue and disability depends on how fatigue is measured. It is only when multidimensional tools are used (MAF, MFSI and FACIT-F) that the effects of fatigue on disability become apparent. The multidimensional fatigue measurements incorporate psychological factors, and had strong correlations with HADS depression and anxiety scores; however, multivariate analyses took these relationships into account and still showed the multidimensional fatigue questionnaires had stronger associations with disability. The results in this thesis suggest fatigue contributes to disability in RA rather than just reflecting psychological factors.

However, it is impossible to determine causality from these results; they cannot differentiate fatigue being disabling from disabled patients being more fatigued. However, there is a complex interaction between fatigue, psychological factors and disability, and this interaction explains why multidimensional tools perform better than the unidimensional VAS in predicting disability.

7.1.3.4. Fatigue Questionnaires

One of the difficulties of studying fatigue in RA is the lack of agreement over which is the best measure of fatigue in RA. Different studies often use different fatigue tools meaning that comparison between studies is difficult. There is also a lack of agreement by what is actually meant by fatigue and what it is that is actually measured using current questionnaires. Many of the studies in this thesis used a simple visual analogue scale for fatigue which has the advantage of being quick and easy to administer and score as well as three different fatigue questionnaires. The

MAF was designed specifically for RA patients so has the advantage of being disease specific, the FACIT-F has been widely used and seems to be the fatigue questionnaire of choice in many drug trials. The MFSI is one of the more comprehensive tools.

There was a strong correlation between all three multidimensional questionnaires; however, the link was less strong with the fatigue VAS. Factor analysis showed fatigue involved five factors or dimensions. These comprised psychological, distress/cognition, severity, physical and social interference. These five factors/dimensions are similar to the dimensions described by the Bristol research group who have recently designed a new fatigue measure for RA [Nicklin et al. 2010]. Their dimensions included living (questions on physical and social interference), cognition, emotion and physical (questions on physical interference and severity). Although five important dimensions were identified none of the questionnaires measured all of them. Questionnaires were often heavily weighted to one domain over another. The FACIT-F was predominantly measuring cognition; MFSI was predominantly measuring psychological factors and the MAF was predominantly measuring the impact of fatigue (physical and social interference).

As five important factors/dimensions of fatigue have been identified an ideal fatigue questionnaire for RA should include all five dimensions/factors. Using statistics and clinical judgement 18 questions were compiled which cover all dimensions which would make an appropriate questionnaire. To determine the usefulness of the suggested items; the questionnaire would need to be subject to test and retest as well as checks for internal consistency and validity. Further research is needed in this area.

7.1.3.5. Fibromyalgic RA

The research in this thesis confirms previous reports that 10–20% of RA patients attending specialist units have fibromyalgic RA. All centres evaluating fibromyalgic RA report similar frequencies in patients attending specialist centres. Recent work from Ranzolin et al, [2009] also showed that high DAS-28 scores are common in patients with fibromyalgia and RA, and Wolfe [Wolfe 2009] suggested the term

‘fibromyalginess’ applied to such patients whom he considered to have polysymptomatic distress. The balance of evidence suggests that there is a subset of RA patients with a fibromyalgic phenotype who have high pain levels unrelated to synovial inflammation, high fatigue scores and more disability with high HAQ scores.

Conventional core data set measures can be used to identify patients with fibromyalgic RA. Such patients have disproportionately high tender joint counts, and can readily be identified by examining tender minus swollen joint counts. A related question is whether in this context fibromyalgia is a separate associated disease or a symptom complex; there is much in favour of the latter approach. Overall patients with high tender joint counts but few swollen joints differ from the majority of patients with relatively equal numbers of tender and swollen joints. Such patients with a pattern of fibromyalgic RA may need a different approach to symptom control and may require a greater emphasis on exercise and psychological treatment and less emphasis on DMARDs alone.

Using DAS-28 ≥ 5.1 to define active RA has the benefits of simplicity and reproducibility. However, these results show that it may overestimate the activity of patients with fibromyalgic RA. The classic entry criteria for trials involve patients having high swollen joint counts [Kingsley et al. 2005] and therefore avoid entering patients with a purely fibromyalgic pattern of disease.

Some patients with many tender points and high tender joint counts who have features of fibromyalgic RA and DAS-28 ≥ 5.1 also have evidence of synovial inflammation with high swollen joint counts. Assessing disease activity in fibromyalgic RA is clearly challenging and complex [Mäkinen et al. 2009]. However, using DAS-28 ≥ 5.1 as the sole criterion to define active RA is too simple and will misclassify a substantial number of patients.

When looking at the effect of treatment on patients with fibromyalgic RA both patients with early and established disease had improvements across most variables of the DAS28, however, despite treatment these patients still had significantly higher DAS28 and HAQ scores following treatment compared to those patients who did not

have fibromyalgic RA. These findings add weight to the argument that other treatments besides conventional treatments are needed in order to reduce DAS28 scores and disability as measured by the HAQ.

7.1.3.6. Pain in RA

Pain thresholds vary substantially in RA patients and are affected by many clinical variables. The dominant factors are high tender point counts, reflecting the presence of fibromyalgic RA [Wolfe et al. 2004; Ranzolin et al. 2009], and prolonged disease duration, which probably reflects central sensitisation.

The association of low pain threshold with disease duration was particularly marked in patients with RA of more than ten years duration and was not just associated with age. This finding suggests that over time the burden of inflammation in RA causes not only progressive joint damage and functional decline but also can lead to persistence of pain. It implies that chronic RA inflammation results in persisting nociceptive stimulation, resulting in central sensitisation and reduced pain thresholds.

Early and intensive treatment which minimises inflammation is likely to reduce central sensitisation and minimise long-term RA pain. Traditional analgesics may have limited value in patients for whom pain remains a problem despite apparent control of their synovitis. Their pain management should focus on treatments that are effective in the presence of central sensitisation.

7.1.4. Treatment Changes

7.1.4.1. Temporal Changes in RA

DAS28 has fallen significantly over the years from a mean of 5.01 in 1997 to a mean of 3.77 in 2010. Individual components of the DAS28 also showed reductions over time though most plateaued from 2006 (swollen joint count, patient global assessment) or 2008 (tender joint count, ESR) onwards. These improvements in DAS28 could be explained by the change in treatment strategies which have very much shifted to treating early and attaining tight control of disease.

Fibromyalgic RA does seem to have decreased over time and whether this reflects the effects of better treatment is unclear. Those patients with fibromyalgic RA continue to have high DAS28 scores which have not changed over time, as opposed to non-fibromyalgic RA patients who showed a gradual and significant reduction in DAS28 over time.

The improvements in DAS28 are mirrored by the increase in the use of combination therapies. There was a non sustained increase in the use of steroids between 1997 and 2003; both of these findings likely reflect studies published around this time. The only drugs which saw a reduction over time were anti-inflammatory drugs, the reason for which is likely due to the withdrawal of Vioxx (rofecoxib) and the concern over their association with increased cardiovascular disease.

The study also showed an increase in biologic use since 2003, although it has not changed significantly since 2006, which would fit with the approval and guidance from NICE in 2002 [NICE TA36]. The plateau in use of biologics in our cohorts may reflect the fact that although there are more treatments available in RA these drugs remain expensive and are currently only used under guidance from NICE in the UK and in the current economic climate there is likely to be pressure on the prescription of these expensive drugs. It is therefore essential to focus more closely on the use of combination therapies and there are current studies underway looking at the efficacy of combination therapy versus biologic therapy which may have important economical impacts.

7.1.4.2. Treatment Decisions

Despite improvements in disease activity scores over the last 15 years, many patients still have active disease. The treatment decisions study showed that only 34% of patients had a change in treatment when seen in the clinic. Although patients with higher DAS28 were more likely to have changes in treatment, the chance of having a treatment change only approached 100% when the DAS28 was over 7.0. More concerning was the lack of treatment change in patients with moderate/intermediate disease activity; only 31% of patients with moderate disease had a change in treatment.

Several reasons might explain the apparent lack of treatment changes, including patient choice, concomitant disease limiting DMARD use or intolerance to DMARDs. The effect of fibromyalgic RA is complex. The results show that if a patient has fibromyalgic RA there is a greater chance overall of having a change in treatment, but this effect is only seen with changes in treatments involving steroids and biologics. Fibromyalgic RA patients had higher DAS28 scores compared to non-fibromyalgic RA and the increased chance of having a change in treatment may be explained by this observation. If treatment changes are led only by DAS28 then it would not be surprising to see an increase in the number of fibromyalgic patients given biologics. Some clinicians however, may use clinical judgment rather than DAS28 to solely determine treatment changes and this may explain why some patients with apparently active disease as measured using a DAS28 do not have their treatment changed.

Treatment decisions were influenced more by objective signs of inflammation (swollen joint count and ESR) and also patient global assessment than by tender joint counts. The multivariate analysis also showed that age has an effect on treatment decisions which retained significance in the multivariate analysis. This suggests that older patients were less likely to have changes in treatment. The possible reasons for this may be that clinicians are willing to accept a degree of disease activity in the older population, and feel that the burden of disease progression and disability will be less than a younger patient. In addition older patients are likely to have more co-

morbidities. Another potential reason is patient choice, which was not explored in this study.

7.2. STRENGTHS AND WEAKNESSES

7.2.1. Strengths

The research in this thesis considered the problems involved in delivering high quality care from a range of perspectives, including those of the patients and the different clinicians involved in care. It also combined qualitative and quantitative research studies and involved many different stakeholders. Finally it looked at the same set of problems using a range of different research methods, which all gave broadly similar findings. These are substantial strengths and they all mean that the conclusions reached are likely to be both robust and reliable.

7.2.2. Weaknesses

Inevitably, the research also has a number of potential weaknesses. Firstly, there was no single hypothesis. Each study had its own hypothesis, or explored a specific theme or set of themes. However the absence of a single hypothesis is intellectually regrettable, even though the very nature of the problem being investigated meant that a unified single question was inappropriate.

Secondly, only limited longitudinal data were collected in the thesis. In research undertaken primarily by the candidate it is impractical to collect data over 3-5 years or longer and data collected from patients followed for shorter periods of time is of less value. Nevertheless, longitudinal data is always helpful in assessing long-term diseases in which there are temporal variations due to the impact of treatment. In the standards of care study and the qualitative studies patients were asked to recall events from the past which inevitability may lead to recall bias.

Thirdly, the findings are regionally focused, and reflect experience in South East London which has a diverse ethnic mix. National data might give a somewhat different perspective and is inevitably preferable as a basis for national recommendations, even though it cannot be collected by a single investigator.

Fourthly, the data is observational and does not include evidence from clinical trials. This reflects the nature of the research questions, which could not be addressed in randomised controlled trials. However, the results have generated hypotheses that can be tested in trials, as outlined below.

Fifthly, there is always a question of representativeness. Although large numbers of patients were used in most parts of the study there were small numbers in the qualitative studies as is often the case in these types of studies and patient selection strived to produce an appropriate and representative cohort. In the fibromyalgic RA studies only the initial cohort had an assessment for the ACR tender points, although the formula to identify patients using standard RA assessments was developed from this cohort. Clearly the tender minus swollen joint counts formula is not a perfect measure but may aid clinicians to identify some of these patients with worse outcomes and perhaps go on to formally assess for fibromyalgic tender points as well as think about possible psychological issues.

Finally, the views on much of the research findings are based on the judgement of the researcher and collaborators, and are not based on absolute measures. Questions such as how much fatigue is too much and the point at which to divide patients into fibromyalgic and non-fibromyalgic RA reflect the views of the researcher rather than any absolute divisions that would be inevitably agreed by all experts in the field. Again, this reflects the nature of the research questions, which all involve relative judgments.

7.3. FUTURE RESEARCH

As most issues discussed in this thesis are not RA pathogenesis related and may in fact be inherent in many other chronic diseases; collaborative work with other researchers looking into the provision of care and whether symptoms such as fatigue are similar in RA and other diseases such as chronic obstructive pulmonary disease or diabetes is something that may be worth addressing in future studies. These studies could also assess differences in provision and expectations of care in different settings such as private health care compared to the NHS.

7.3.1. Better Treatment of Fatigue and Pain

From our research it is clear that fatigue remains a major issue for RA patients. Currently there are no treatments that specifically target fatigue in RA. There is some evidence that DMARDS and biologics have some effect on fatigue in RA [Chauffier et al. 2012] but they are specifically targeting inflammation in RA. Cognitive behavioural therapy (CBT) has been used with effect in other diseases where fatigue is a prominent symptom such as multiple sclerosis [van Kessel et al. 2008]. In chronic fatigue syndrome, where fatigue is the dominant feature CBT and graded exercise have been shown to improve fatigue [White et al. 2011].

A recent study by Hewlett et al [Hewlett et al. 2011; Dures et al. 2011]; used group CBT to target fatigue in RA patients. Patients with high fatigue (VAS >60mm) were randomised into one of two groups; group CBT for six sessions weekly and a consolidation session or the control group who received fatigue self management information in a one hour didactic group session. At 18 weeks significant improvements were seen in fatigue measured by the MAF and VAS in the active group compared to the control group. In addition, there were significant improvements in disability, depression, helplessness, self-efficacy and sleep scores.

Following on from this research, a proposal has been put together for a trial designed to improve fatigue and disability in RA. The CEFRAD Trial (Cognitive Behavioural Therapy and Exercise to Improve Fatigue and Rheumatoid Arthritis Disability); is designed to develop and evaluate a treatment programme consisting of cognitive behavioural therapy and exercise advice that can be provided within the rheumatology outpatient department by trained rheumatology specialist nurses. The aim of the study will be to reduce fatigue levels in RA patients with high levels of fatigue and also reduce disability as measured by the HAQ. The study duration is for six months and patients will be randomised into one of two arms. The active arm of the study will involve individual CBT and exercise advice and the control arm will consist of standard treatment as defined by NICE guidance. The outline proposal for the trial is shown in Table 7.1

Table 7:1 Outline Proposal for Fatigue Trial

Proposed Research
Cognitive Behavioural Therapy And Exercise To Improve Fatigue and Rheumatoid Arthritis Disability: The CEFRAD Trial
Goal
To develop and evaluate a treatment programme of cognitive behavioural therapy (CBT) with advice about exercise given by rheumatology nurses in routine care which treats high fatigue levels in patients with rheumatoid arthritis (RA)
Rationale
<ul style="list-style-type: none"> a. CBT and exercise reduce fatigue and disability in many long-term disorders (eg chronic fatigue syndrome and systemic lupus erythematosus) b. Many RA patients have high fatigue levels which are associated with high pain and disability scores c. Few RA patients currently receive treatment designed to specifically reduce fatigue
Hypothesis
CBT with exercise advice given by rheumatology nurses will minimise fatigue and gives sustained, clinically important improvements in disability in RA patients with high levels of fatigue
Objectives
<p>Experience from observational studies and clinical trials to improve fatigue will be used to develop a treatment for RA fatigue which combines CBT with advice on exercise which delivered by specialist nurses. A large clinical trial will establish its effectiveness by showing it:</p> <ul style="list-style-type: none"> a. Gives clinically relevant reductions in fatigue and disability b. Achieves improvements sustained for 6 months c. Delivers cost-effective improvements
Design And Setting
6-month individually-randomised 2-arm pragmatic multicentre trial based in rheumatology out-patients
Target Population
<ul style="list-style-type: none"> a. Included: RA by current criteria; high fatigue (FACIT F <15); stable drug/biologics therapy; willing/able to participate a. b. Excluded: remission; major co-morbidities, pregnancy; irreversible disability (>20 years RA)
Health Technologies Assessed
<ul style="list-style-type: none"> a. Active: CBT and exercise advice from specialist nurses to individual RA patients b. "Standard Care": NICE 2009 guidelines
Measurement Of Cost And Outcomes
<ul style="list-style-type: none"> a. Co-primary Outcomes: Fatigue on multidimensional instrument (FACIT-F) and disability assessment health assessment questionnaire (HAQ) b. Clinical: pain (visual analogue score), disease activity score for 28 joints, hospital anxiety and depression score c. Quality of life: SF-36 and EuroQol

d. Costs: Client Service Receipt Inventory
Sample Size And Analysis
The hypothesis (CBT/exercise reduce fatigue and improve disability) requires improvements in HAQ levels of 0.22 (smallest clinically detectable change) at 6 months (published SD for change 0.55). Showing this with 5% significance and 90% power means recruiting 133 patients per group (266 in total); allowing for 20% drop-outs means recruiting 320 patients. Analysis will involve linear regression adjusted for age, gender and initial scores

7.3.2. Adherence to Guidance and Developing Clinical Pathways

The research shows that patients with active disease ($\text{DAS28} \geq 5.1$) more often than not have a change in their treatment, however, there is a large group of patients with disease activity that falls into the intermediate category of disease activity that don't have a change in treatment. The reason for this apparent lack of treatment change is not apparent and may be due to patient choice, concomitant diseases or other factors such as fatigue or psychological factors which may be contributing to the DAS28.

The work has been used to develop a new research programme (Treatment Intensities and Targets in RA Therapy Integrating Patients' and Clinicians' Views – The TITRATE Programme). This programme includes a randomised trial which specifically targets patients with intermediate disease activity to provide an intensive management strategy that includes not only increases in drug therapy but also employs self –management as well as ‘motivational interviewing’ techniques. Patients will be involved in each step to improve compliance and a written care plan provided. Psychosocial aspects, quality of life and fatigue will also be assessed. The outline proposal for the trial is shown in Table 7.2 and depicted in Figures 7.1 and 7.2.

**Table 7:2 Treatment Intensities and Targets in RA Therapy
Integrating Patients' and Clinicians' Views – The TITRATE Programme**

Objectives
<p>The overall objective is a patient-led implementation of an effective intensive management strategy for RA patients with intermediate disease activity. The aims comprise:</p> <ol style="list-style-type: none"> Equipping patients to benefit from intensive management Understanding patients' views about it Implementing it in routine care in partnership with patients
Goals
<p>As intensive management will be challenging for RA patients, its effectiveness will depend on equipping them to benefit from receiving it. This will involve the following:</p> <ol style="list-style-type: none"> Developing information that enables patients understand intensive management Establishing shared care plans which involve patients in planning their treatment ("no decision about me without me"). These will build on Joint Crisis Plans, which help patients with major mental health disorders choose treatments and the National Rheumatoid Arthritis Society (NRAS) Members' Care Plan developed by patients for patients. The shared treatment plans for RA will involve agreements about drugs, dosages and therapeutic sequences. Training specialist nurses to support patients. One part will involve understanding psychosocial issues - illness beliefs, self-efficacy, adherence, beliefs about medicine, fatigue and anxiety and depression. The other part will involve improving adherence.
Design And Setting
12-month pragmatic open label multicentre trial with individual randomisation based in specialist rheumatology clinics in England.
Hypothesis
Patients with RA for at least 6 months who have intermediate disease activity (DAS28 3.2-5.1) after receiving at least one DMARD will be more likely to achieve remission over 12 months if they receive intensive management (combination DMARDs with or without biologics) than standard care (NICE guidelines 2009).
Target Population
<ol style="list-style-type: none"> Inclusion Criteria: RA by current classification criteria; received ≥ 1 DMARD(s) for ≥ 6 months; intermediate disease activity (DAS28 3.2-5.1); willing and able to follow intensive management programme Exclusion Criteria: major co-morbidities making intensive treatment inadvisable (eg heart failure); previously failed multiple DMARDs (≥ 5 treatments) or having received biologics; irreversible disability from extensive joint damage (disease duration ≥ 20 years); pregnancy, breast-feeding and women at risk of conceiving
Intensive Management
<ol style="list-style-type: none"> Approach: patients will be seen monthly by trained specialist nurses who will assess their RA, evaluate treatments, modify therapy, and give supportive care outlined above in "Equipping Patients To Benefit From Intensive Management"

<ul style="list-style-type: none"> b. Screening: Eligibility will be checked and disease activity assessed c. Supportive information: this will be provided after screening through the patient handbook and psychosocial factors measured using self-assessment instruments for illness beliefs, self-efficacy and adherence and anxiety and depression. Advice will also be given on how to self-manage pain by optimising analgesics and NSAIDs. d. Initial visit (within 2 weeks): disease activity will be assessed, a “Shared Care Plan” agreed between patients and specialist nurses, and the first treatment change initiated using the DMARD/Steroid treatment algorithm. This will involve starting another DMARD with additional IM steroids if relevant. e. Visits 2-5: disease activity will be assessed and treatment stepped up following the agreed treatment algorithm. Patients will be encouraged to self manage pain. Adherence will also be encouraged using “Motivational Interviewing” approaches. f. Patients in remission ($\text{DAS28} < 2.6$) after visit 1: treatment will be sustained at its present level until month 12 unless there is a subsequent increase in activity. g. Patients with major flare ($\text{DAS28} > 5.1$) after visit 1: considered for biologic therapy with TNF inhibitor, which requires safety screen and second visit one month later to ensure flare persists. h. Visit 6: “intermediate assessment” on basis of assessment of disease activity will divide patients into 3 groups: good response (DAS28 fell by > 1.2) - maintain approach and increase current DMARDs; partial response (DAS28 fell by $0.6 - 1.2$) - initiate new DMARDs; no response (DAS28 fell by < 0.6 and ≥ 3 swollen/tender joints - initiate TNF inhibitor after safety screen i. Visits 7-11: disease activity will be assessed and treatment stepped up using agreed treatment algorithm j. Final visit: on the basis of assessments of disease activity patients will be divided into three groups – remission/low disease activity, ongoing intermediate disease activity, or flare requiring biologics. Self-assessment instruments for illness beliefs, self-efficacy and adherence and anxiety and depression will also be recorded k. The patients in remission/ low disease activity will be offered treatment tapering in a pilot trial. Other patients will thereafter receive standard care, with patients on biologics due to flare remaining on these treatments (current NICE guidance)
"Standard Care" (based on NICE 2009 guidelines)
<ul style="list-style-type: none"> a. Maintain suppressive treatment with DMARDs and steroids b. Maintain symptomatic therapy (analgesics/non-steroidal anti-inflammatory drugs) c. Annual specialist reviews d. Urgent specialist review and treatment modification for flares ($\text{DAS28} \geq 5.1$) or clinically significant adverse events
Assessments
<p><i>Baseline assessments will comprise:</i></p> <ul style="list-style-type: none"> a. Demographic data (age, gender, ethnicity, Townsend score) b. Current and previous treatments for RA c. Features of RA (disease duration, rheumatoid factor positivity, erosions) d. Extra-articular RA e. Co-morbidities f. Relevant psychosocial factors: health belief (revised RA specific Illness Perception Questionnaire) and depression and anxiety (Hospital Anxiety and

<p>Depression Score)</p> <p>g. Adherence by Medication Adherence Rating Scale (MARS) and fatigue by the FACIT-F.</p> <p><i>Co-primary outcomes will comprise:</i></p> <p>a. The number of patients achieving remission by DAS28 ≤ 2.6</p> <p>b. The number of patients achieving remission by SDAI ≤ 3.3</p> <p>Secondary outcomes will comprise:</p> <p>a. Tender/swollen joint counts (28 joints), patient/assessor global assessment, ESR and CRP used to calculate DAS28, SDAI and CDAI</p> <p>b. HAQ</p> <p>c. SF36 and EuroQol</p> <p>d. Erosive damage: x-rays of hands and feet read by modified Larsen's score</p> <p>e. Adverse events</p> <p>f. Health resource use questionnaire</p>
<p>Sample Size</p> <p>The most relevant UK trial (TICORA) compared tight control versus standard treatment in patients with RA for less than 5 years. It reported 16% of patients receiving standard care achieved DAS remission at the end of the trial. Patients receiving standard treatment showed decreases in DAS until 12 months but no further falls from 12-18 months. Analysis of routine care patients from the King's Health Partners database showed 16% of those patients with initial intermediate disease activity treated with DMARDs were in remission at their second visit between 9-15 months. We have also analysed all similar RA trials that reported remission, including our early RA CARDERA trial. These show that overall with standard care 16% of patients will have achieved DAS remission at 1 year follow-up. We also anticipate intensive treatment should almost double the rate of remission (increase rates by at least 15%).</p> <p>We will reject the null hypothesis (RA patients with intermediate disease activity (DAS28 3.2-5.1) despite DMARDs will not have no more remissions with intensive management for 12 months) if the difference in remission rates at 12 months between the intensive management arm and the standard care arm is 15% or greater. Demonstrating such a difference with 5% significance and 90% power requires randomising 358 patients in total, under 1:1 allocation (i.e. 179 patients per group). After allowance is made for a 10% drop-out overall, the required total sample size increases to 398 patients. Although the CARDERA trial suggests DAS28 and SDAI remissions occur with similar frequencies, there is limited comparative data for SDAI remission; we therefore based sample size calculations on DAS28 remissions.</p>
<p>Analysis</p> <p>An intention-to-treat analysis will be used to determine whether there is a difference in remission rates between arms of this pragmatic randomised trial. Missing data will be dealt with primarily through use of multiple imputation, though other approaches to assess the impact of "missingness" may be adopted for additional sensitivity analyses. The primary outcome – remission at 12 months – will be modelled using logistic regression methods. Adjustment for a centre effect in all analyses will be performed. Additional adjustment by demographic and clinical factors will also be investigated.</p>

Figure 7:1 Synopsis of Current Specialist Management

Current Specialist Management Of Established Rheumatoid Arthritis

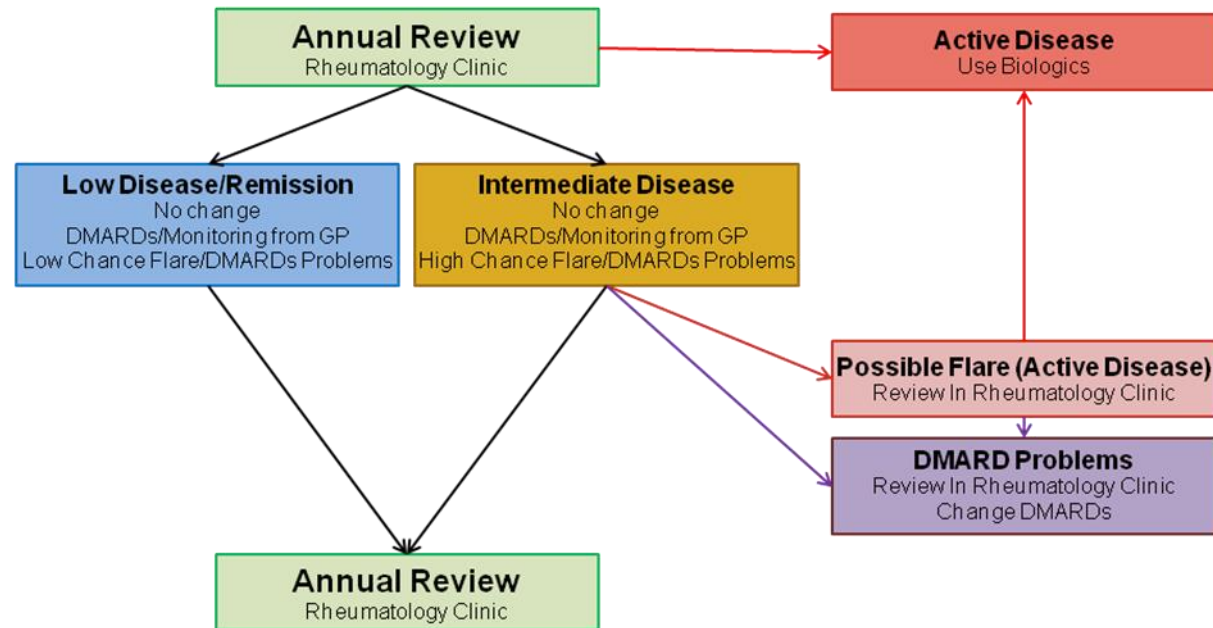
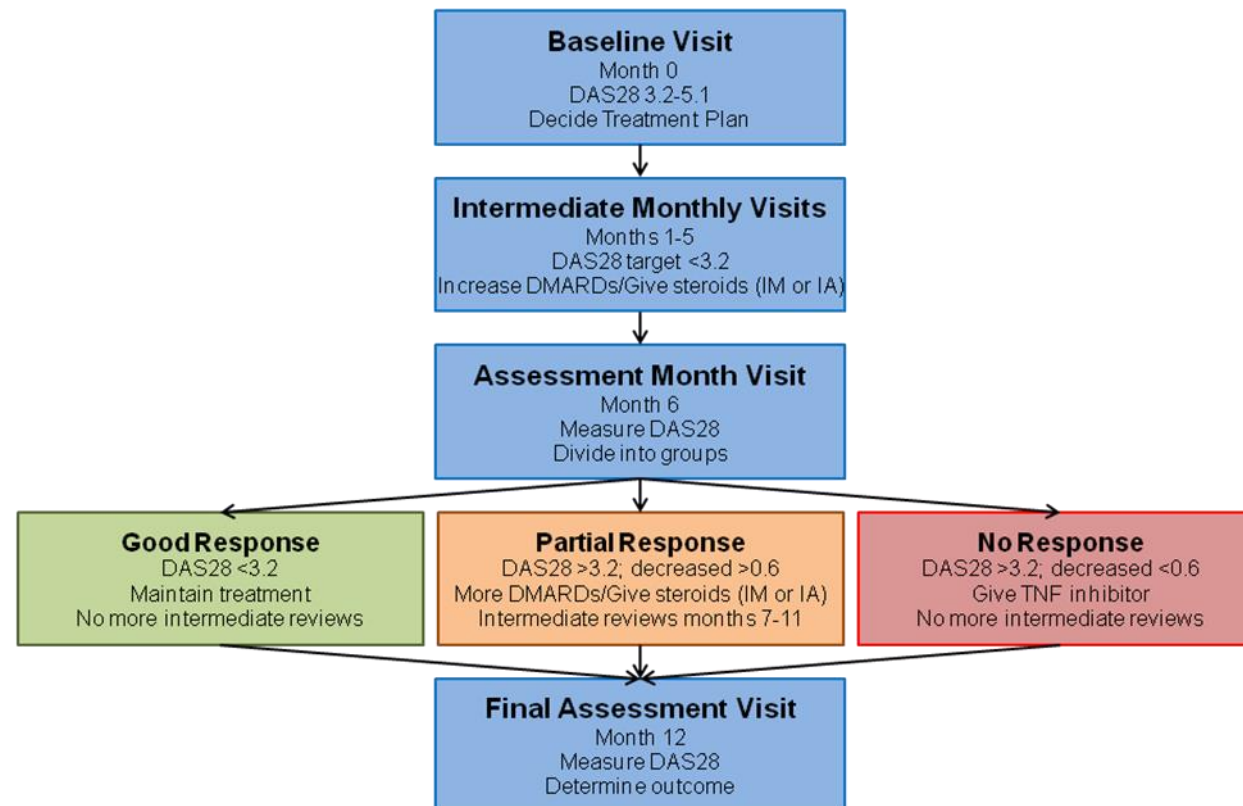


Figure 7:2 Outline of Active Treatment in TITRATE Programme

Active Management In Pragmatic Trial Of TITRATE Programme



7.3.3. Other Approaches

The treatment of RA has changed dramatically in the last two decades and the speed of change has, if anything increased. In the UK the new regulatory environment and the existence of standards of care such as the new NICE guidelines for RA have been of crucial importance [Deighton et al. 2009; Deighton et al. 2010a; Deighton et al. 2010b]. There is a growing recognition that non-drug therapy is equally as important as drug therapy, though this area is far less researched. Other areas which need developing include understanding the importance of exercise [Bearne et al. 2002], promoting sleep for arthritis [Ulus et al. 2011], focusing on regional problems such as foot disease [Otter et al. 2011; Otter et al. 2012], and moving from hospital based care to care in the community [Symmons et al. 2005; Davies et al. 2007]. The research in this thesis contributes to setting this new agenda for ongoing change. Although RA care has improved there is a pressing need for further improvement in years to come.

REFERENCES

- Ahlmen M, Nordenskiöld U, Archenholtz B, Thyberg I, Rönqvist R, Lindén L, Andersson AK, Mannerkorpi K. 2005, Rheumatology outcomes: the patient's perspective. A multicentre focus group interview study of Swedish rheumatoid arthritis patients. *Rheumatology*. 44:105-10.
- Alamanos Y, Voulgari PV, Drosos AA. 2006, Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum*. 36: 182-8.
- Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G. 2010, Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 62: 2569-81.
- Altman DG, Bland JM. 1994, Diagnostic tests 3: receiver operating characteristic plots. *BMJ*. 309(6948):188.
- Anderson DL. 2001, Development of an instrument to measure pain in rheumatoid arthritis: Rheumatoid Arthritis Pain Scale (RAPS). *Arthritis Rheum*. 45: 317-23.
- Anderson J, Sayles H, Curtis JR, Wolfe F, Michaud K. 2010, Converting modified health assessment questionnaire (HAQ), multidimensional HAQ, and HAQII scores into original HAQ scores using models developed with a large cohort of rheumatoid arthritis patients. *Arthritis Care Res (Hoboken)*. 62(10):1481-8.
- Anderson KO, Bradley LA, Young LD, McDaniel LK, Wise CM. 1985, Rheumatoid arthritis: review of psychological factors related to etiology, effects, and treatment. *Psychol Bul*. 98: 358-87.
- ARMA: <http://www.arma.uk.net/>
- ARMA Standards of Care for people with inflammatory arthritis 2004. <http://arma.uk.net/wp-content/uploads/pdfs/ia06.pdf>
- ARMA Standards of Care for people with osteoarthritis 2004. <http://arma.uk.net/wp-content/uploads/pdfs/oa06.pdf>
- ARMA Standards of Care for people with back pain 2004. <http://arma.uk.net/wp-content/uploads/pdfs/bp06.pdf>
- ARMA Standards of Care for people with connective tissue diseases 2007. <http://arma.uk.net/wp-content/uploads/pdfs/ctdweb.pdf>
- ARMA Standards of Care for people with metabolic bone diseases 2007. <http://arma.uk.net/wp-content/uploads/pdfs/mbdweb.pdf>
- ARMA Standards of Care for people with regional musculoskeletal pain 2007. <http://arma.uk.net/wp-content/uploads/pdfs/rmpweb.pdf>

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, Medsger TA, Mitchell DM, Neustadt DH, Pinals RS, Schaller JG, Sharp JT, Wilder RL, Hunder GG 1988 The American Rheumatism Association 1987, revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 31: 315-24.

Arnold R, Ranchor AV, Sanderman R, Kempen GI, Ormel J, Suurmeijer TP. 2004, The relative contribution of domains of quality of life to overall quality of life for different chronic diseases. *Qual Life Res.* 13: 883-96.

Arts E, Fransen J, Lemmers H, Stalenhoef A, Joosten L, van Riel P, Popa CD. 2012, High-density lipoprotein cholesterol subfractions HDL2 and HDL3 are reduced in women with rheumatoid arthritis and may augment the cardiovascular risk of women with RA: a cross-sectional study. *Arthritis Res Ther.* 14: R116.

Atzeni F, Cazzola M, Benucci M, Di Franco M, Salaffi F, Sarzi-Puttini P. 2011, Chronic widespread pain in the spectrum of rheumatological diseases. *Best Pract Res Clin Rheumatol.* 25: 165-71.

Balsa A, Carmona L, Gonzalez-Alvaro I, Belmonte MA, Tena X, Sanmartí R; EMECAR Study Group. 2004, Value of Disease Activity Score 28 (DAS28) and DAS28-3 compared to American College of Rheumatology-defined remission in rheumatoid arthritis. *J Rheumatol.* 31: 40-6.

Barlow JH, Cullen LA, Rowe IF. Comparison of knowledge and psychological well-being between patients with a short disease duration (< or = 1 year) and patients with more established rheumatoid arthritis (> or = 10 years duration). *Patient Education & Counseling.* 1999; 38: 195–203.

Bath J, Hooper J, Giles M, Steel D, Reed E, Woodland J. 1999, Patient perceptions of rheumatoid arthritis. *Nursing Standard.* 14: 35–38.

Bearne LM, Scott DL, Hurley MV. 2002, Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity. *Rheumatology.* 41: 157-66.

Beck AT, Ward CH and Mendelson M, Mock J, Erbaugh J. 1961, An inventory for measuring depression, *Arch Gen Psychiatry.* 4: 561-71.

Bell C, Rowe IF. 2011, The recognition and assessment of cardiovascular risk in people with rheumatoid arthritis in primary care: a questionnaire-based study of general practitioners. *Musculoskeletal Care.* 9: 69-74.

Belza BL, Henke CJ, Yelin EH, Epstein WV, Gilliss CL. 1993, Correlates of fatigue in older adults with rheumatoid arthritis. *Nurs Res.* 42: 93-9.

Belza BL. 1995, Comparison of self-reported fatigue in rheumatoid arthritis and controls. *J Rheumatol.* 22: 639-43.

Bentsen SB, Gundersen D, Assmus J, Bringsvor H, Berland A. 2013, Multiple symptoms in patients with chronic obstructive pulmonary disease in Norway. *Nurs Health Sci.* In press

Bernatsky S, Feldman D, De Civita M, Haggerty J, Tousignant P, Legaré J, Zummer M,

- Meagher T, Mill C, Roper M, Lee J. 2010, Optimal care for rheumatoid arthritis: a focus group study. *Clin Rheumatol.* 29: 645-57.
- Birrell FN, Hassell AB, Jones PW, Dawes PT. 2000, How does the short form 36 health questionnaire (SF-36) in rheumatoid arthritis (RA) relate to RA outcome measures and SF-36 population values? A cross-sectional study. *Clin Rheumatol.* 19: 195-9.
- Black J, Lewis T, McIntosh P, Callaly T, Coombs T, Hunter A, Moore L. 2009, It's not that bad: the views of consumers and carers about routine outcome measurement in mental health. *Aust Health Rev.* 33: 93-9.
- Bliddal H, Danneskiold-Samsøe B. 2007, Chronic widespread pain in the spectrum of rheumatological diseases. *Best Pract Res Clin Rheumatol.* 21: 391-402.
- Brennan P, Silman A. 1994, Breast-feeding and the onset of rheumatoid arthritis. *Arthritis Rheum.* 37: 808-13.
- Britten N. 1995, Qualitative interviews in medical research. *BMJ.* 311: 251-253.
- Bruce B, Fries JF, Murtagh KN. 2007, Health status disparities in ethnic minority patients with rheumatoid arthritis: a cross-sectional study. *J Rheumatol.* 34: 1475-9.
- Bryman, A. 1988, *Quantity and Quality in Social Research.* Unwin Hyman: London.
- Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, Khraishi M, Leclercq SA, Légaré J, Mosher DP, Pencharz J, Pope JE, Thomson J, Thorne C, Zimmer M, Bombardier C. 2012, Canadian Rheumatology Association Recommendations for Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-modifying Antirheumatic Drugs. *J Rheumatol.* 39: 1559-82.
- Carr A, Hewlett S, Hughes R Mitchell H, Ryan S, Carr M, Kirwan J. 2003, Rheumatology outcomes: the patient's perspective. *J Rheumatol.* 30(4):880-3.
- Cavagna L, Boffini N, Cagnotto G, Inverardi F, Grosso V, Caporali R. 2012, Atherosclerosis and rheumatoid arthritis: more than a simple association. *Mediators Inflamm.* 2012: 147354.
- Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. 2005, Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol.* 32: 811-9.
- Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J. 1993, The Functional Assessment of Cancer Therapy scale: development and validation of the general measure *J Clin Oncol.* 11: 570-9.
- Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, Wallace EP. 1993, Development of a fatigue scale. *J Psychosom Res.* 37: 147-53.
- Chard J, Dickson J, Tallon D, Dieppe P. 2002, A comparison of the views of rheumatologists, general practitioners and patients on the treatment of osteoarthritis. *Rheumatology (Oxford).* 41: 1208-1210.

- Chauffier K, Salliot C, Berenbaum F, Sellam J. 2012, Effect of biotherapies on fatigue in rheumatoid arthritis: a systematic review of the literature and meta-analysis. *Rheumatology (Oxford)*. 51: 60-8.
- Choy E. 2012, Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. *Rheumatology (Oxford)*. 51 Suppl 5:v3-11.
- Choy EH, Hazleman B, Smith M, Moss K, Lisi L, Scott DG, Patel J, Sopwith M, Isenberg DA. 2002, Efficacy of a novel PEGylated humanized anti-TNF fragment (CDP870) in patients with rheumatoid arthritis: a phase II double-blinded, randomized, dose-escalating trial. *Rheumatology*. 41: 1133-7.
- Choy EH, Panayi GS. 2001, Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med*. 344: 907-16.
- Choy EH, Smith CM, Farewell V, Walker D, Hassell A, Chau L, Scott DL; CARDERA (Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis) Trial Group. 2008, Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. *Ann Rheum Dis*. 67: 656-63.
- Clark P, Lavielle P, Martinez H. 2003, Learning from pain scales: patient perspective. *J Rheumatol*. 30: 1584-8.
- Constantinescu F, Goucher S, Weinstein A, Fraenkel L. 2009, Racial disparities in treatment preferences for rheumatoid arthritis. *Med Care*. 47: 350-5.
- Coury F, Rossat A, Tebib A, Letroublon MC, Gagnard A, Fantino B, Tebib JG. 2009, Rheumatoid arthritis and fibromyalgia: a frequent unrelated association complicating disease management. *J Rheumatol*. 36: 58-62.
- Crosby LJ. 1991, Factors which contribute to fatigue associated with rheumatoid arthritis. *J Adv Nurs*. 16: 974-81.
- Currey SS, Rao JK, Winfield JB, Callahan LF. 2003, Performance of a generic health-related quality of life measure in a clinic population with rheumatic disease. *Arthritis Rheum*. 49: 658-64.
- Da Silva JA, Spector TD. 1992, The role of pregnancy in the course and aetiology of rheumatoid arthritis. *Clin Rheumatol*. 11: 189-94.
- Darzi A. 2008, High Quality of Care for All. London: Department of Health.
- Davies LM, Fargher EA, Tricker K, Dawes P, Scott DL, Symmons D. 2007, Is shared care with annual hospital review better value for money than predominantly hospital-based care in patients with established stable rheumatoid arthritis? *Ann Rheum Dis*. 66: 658-63.
- Davis MJ, Dawes PT, Fowler PD, Sheeran TP, Shadforth MF, Ziade F, Collins M, Jones P. 1990, Comparison and evaluation of a disease activity index for use in patients with rheumatoid arthritis. *Br J Rheumatol*. 29: 111-5.
- Deighton C, Hyrich K. 2008, International guidelines on access to biologic therapy: why the differences and which is best? *Nat Clin Pract Rheumatol*. 4: 520-1.
- Deighton C, O'Mahony R, Tosh J, Turner C, Rudolf M; Guideline Development Group.

2009, Management of rheumatoid arthritis: summary of NICE guidance. *BMJ*. 16; 338: b702.

Deighton C, Rudolf M. 2010, How does rheumatoid arthritis need to be managed? *Clin Med*. 10: 151-3.

Deighton C, Scott DL. 2010, Treating inflammatory arthritis early. *BMJ*. 31; 341: c7384.

Dejaco C, Duftner C, Wipfler-Freissmuth E, Weiss H, Graninger WB, Schirmer M. 2011, Similar performance of DAS-28, CDAI, and SDAI in rheumatoid arthritis patients with and without sonographic signs of active inflammation in routine clinical practice. *Scand J Rheumatol*. 40: 234-6.

Department of Health. Musculoskeletal Services Framework. 2006, London: Department of Health.

http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4138413

Department of Health. 2012, Draft Payment by Results Guidance for 2013-14.

<https://www.wp.dh.gov.uk/publications/files/2012/12/Draft-PbR-Guidance-for-2013-14-not-accessible.pdf>

Doeglas D, Suurmeijer T, Krol B, Sanderman R, van Rijswijk M, van Leeuwen M. 1994, Social support, social disability, and psychological well-being in rheumatoid arthritis. *Arthritis Care Res*. 7: 10-5.

Dures E, Kitchen K, Almeida C, Ambler N, Cliss A, Hammond A, Knops B, Morris M, Swinkels A, Hewlett S. 2012, "They didn't tell us, they made us work it out ourselves": Patient perspectives of a cognitive-behavioural programme for rheumatoid arthritis fatigue. *Arthritis Care Res*. 64: 494-501

Edwards JC, Cambridge G. 2001, Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes. *Rheumatology*. 40: 205-11.

Emery P. 1994, The Roche Rheumatology Prize Lecture. The optimal management of early rheumatoid disease: the key to preventing disability. *Br J Rheumatol*. 33: 765-8.

Empl M, Renaud S, Erne B, Fuhr P, Straube A, Schaeren-Wiemers N, Steck AJ. 2001, TNF alpha expression in painful and nonpainful neuropathies. *Neurology*. 56: 1371-7.

Escalante A, del Rincón I. 1999, How much disability in rheumatoid arthritis is explained by rheumatoid arthritis? *Arthritis Rheum*. 42: 1712-21.

EuroQol--a new facility for the measurement of health-related quality of life. 1990, The EuroQol Group. *Health Policy*. 16: 199-208.

Exley C, Field D, Jones L, Stokes T. 2005, Palliative care in the community for cancer and end-stage cardiorespiratory disease: the views of patients, lay-carers and health care professionals. *Palliat Med*. 19: 76-83.

Fautrel B, Flipo RM, Saraux A. 2008, Eligibility of rheumatoid arthritis patients for anti-TNF-alpha therapy according to the 2005 recommendations of the French and British Societies for Rheumatology. *Rheumatology*. 47: 1698-703.

Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, Chernoff M, Fried B, Furst D, Goldsmith C, Kieszak S, Lightfoot R. 1993, The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum.* 36: 729-40.

Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, Katz LM, Lightfoot R Jr, Paulus H, Strand V, Tugwell P, Weinblatt M, Williams HJ, Wolfe F, Kieszak S. 1995, American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* 38: 727-35.

Fifield J, McQuillan J, Tennen H, Sheehan TJ, Reisine S, Hesselbrock V, Rothfield N. 2001, History of affective disorder and the temporal trajectory of fatigue in rheumatoid arthritis. *Ann Behav Med.* 23: 34-41.

Fifield J, Tennen H, Reisine S, McQuillan J. 1998, Depression and the long-term risk of pain, fatigue, and disability in patients with rheumatoid arthritis. *Arthritis Rheum.* 41: 1851-7.

Fiocco U, Sfriso P, Oliviero F, Pagnin E, Scagliori E, Campana C, Dainese S, Cozzi L, Punzi L. 2008, Co-stimulatory modulation in rheumatoid arthritis: the role of (CTLA4-Ig) abatacept. *Autoimmun Rev.* 8: 76-82.

Fisher, M. 1999, Selecting computers for qualitative analysis; in: *IT in Social Sciences: a Students' Guide to the Information and Communication Technologies (ICS)*; H. Millsom ed; Blackwell Publishers: Oxford. Chapter 8.

Flachenecker P, Kümpfel T, Kallmann B, Gottschalk M, Grauer O, Rieckmann P, Trenkwalder C, Toyka KV. 2002, Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Mult Scler.* 8(6):523-6.

Flendrie M, Creemers MC, van Riel PL. 2007, Titration of infliximab treatment in rheumatoid arthritis patients based on response patterns. *Rheumatology (Oxford).* 46: 146-9.

Frank RG, Beck NC, Parker JC, Kashani JH, Elliott TR, Haut AE, Smith E, Atwood C, Brownlee-Duffeck M, Kay DR. 1988, Depression in rheumatoid arthritis. *J Rheumatol.* 15: 920-5.

Fries JF, Bloch DA, Sharp JT, McShane DJ, Spitz P, Bluhm GB, Forrester D, Genant H, Gofton P, Richman S, Weissman B, Wolfe F. 1986, Assessment of radiologic progression in rheumatoid arthritis. A randomized, controlled trial. *Arthritis Rheum.* 29: 1-9.

Fuchs HA, Brooks RH, Callahan LF, Pincus T. 1989, A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis. *Arthritis Rheum.* 32: 531-7.

Furst DE, Halbert RJ, Bingham CO 3rd, Fukudome S, Anderson L, Bonafede P, Bray V, Cohen SB, Sherrer YR, St Clair EW, Tesser JR, Weinblatt M, Dubois RW. 2008, Evaluating the adequacy of disease control in patients with rheumatoid arthritis: a RAND appropriateness panel. *Rheumatology.* 47: 194-9.

Galloway JB, Mercer LK, Moseley A, Dixon WG, Ustianowski AP, Helbert M, Watson KD, Lunt M, Hyrich KL, Symmons DP. 2013, Risk of skin and soft tissue infections

(including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis.* 72: 229-34.

Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Ustianowski AP, Helbert M, Watson KD, Lunt M, Symmons DP; 2011, BSR Biologics Register. Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis.* 70: 1810-4.

Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, Watson KD, Lunt M, Symmons DP; 2011, BSRBR Control Centre Consortium; British Society for Rheumatology Biologics Register. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford).* 50: 124-31.

Gardiner PV, Sykes HR, Hassey GA, Walker DJ. 1993, An evaluation of the Health Assessment Questionnaire in long-term longitudinal follow-up of disability in rheumatoid arthritis. *Br J Rheumatol.* 32: 724-8.

Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT. 1993, The SF-36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *BMJ.* 29; 306: 1440-4.

Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. 2002, Quality of life measurement: bibliographic study of patient assessed health outcome measures. *BMJ.* 324: 1417.

Gerecz-Simon EM, Tunks ER, Heale JA, Kean WF, Buchanan WW. 1989, Measurement of pain threshold in patients with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and healthy controls. *Clin Rheumatol.* 8: 467-474.

Gettings L. 2010, Psychological well-being in rheumatoid arthritis: a review of the literature. *Musculoskeletal Care.* 8: 99-106.

Gibofsky A. 2012, Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. *Am J Manag Care.* 18(13 Suppl): s295-302.

Gladman DD, Urowitz MB, Gough J, MacKinnon A. 1997, Fibromyalgia is a major contributor to quality of life in lupus. *J Rheumatol.* 24: 2145-8.

Goodenow C, Reisine ST, Grady KE. 1990, Quality of social support and associated social and psychological functioning in women with rheumatoid arthritis. *Health Psychol.* 9: 266-84.

Goronzy JJ, Weyand CM. 1993, Interplay of T lymphocytes and HLA-DR molecules in rheumatoid arthritis. *Curr Opin Rheumatol.* 5: 169-77.

Gossec L, Paternotte S, Aanerud GJ, Balanescu A, Boumpas DT, Carmona L, de Wit M, Dijkmans BA, Dougados M, Englbrecht M, Gogus F, Heiberg T, Hernandez C, Kirwan JR, Mola EM, Cerinic MM, Otsa K, Schett G, Scholte-Voshaar M, Sokka T, von Krause G, Wells GA, Kvien TK. 2011, Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid

arthritis: a EULAR initiative. *Ann Rheum Dis.* 70: 935-42.

Greco M, Sweeney K, Brownlea A, McGovern J. 2001, The practice accreditation and improvement survey (PAIS). What patients think. *Aust Fam Physician.* 30: 1096-100.

Greenwood MC, Doyle DV, Ensor M. 2001, Does the Stanford Health Assessment Questionnaire have potential as a monitoring tool for subjects with rheumatoid arthritis? *Ann Rheum Dis.* 60: 344-8.

Griffiths B, Situnayake RD, Clark B, Tennant A, Salmon M, Emery P. 2000, Racial origin and its effect on disease expression and HLA-DRB1 types in patients with rheumatoid arthritis: a matched cross-sectional study. *Rheumatology.* 39: 857-64.

Groarke A, Curtis R, Coughlan R, Gsel A. 2004, The role of perceived and actual disease status in adjustment to rheumatoid arthritis. *Rheumatology.* 43: 1142-9.

Hann DM, Jacobsen PB, Azzarello LM, Martin SC, Curran SL, Fields KK, Greenberg H, Lyman G. 1998, Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. *Qual Life Res.* 7: 301-10.

Hannaford PC, Kay CR, Hirsch S: 1990, Oral contraceptives and rheumatoid arthritis: new data from the Royal College of General Practitioners' oral contraception study. *Ann Rheum Dis.* 49: 744-746.

Haraoui B, Smolen JS, Aletaha D, Breedveld FC, Burmester G, Codreanu C, Da Silva JP, de Wit M, Dougados M, Durez P, Emery P, Fonseca JE, Gibofsky A, Gomez-Reino J, Graninger W, Hamuryudan V, Jannaut Peña MJ, Kalden J, Kvien TK, Laurindo I, Martin-Mola E, Montecucco C, Santos Moreno P, Pavelka K, Poor G, Cardiel MH, Stanislawska-Biernat E, Takeuchi T, van der Heijde D; Treat to Target Taskforce. 2011, Treating Rheumatoid Arthritis to Target: multinational recommendations assessment questionnaire. *Ann Rheum Dis.* 70: 1999-2002.

Harrison B, Symmons D. 2000, Early inflammatory polyarthritis: results from the Norfolk Arthritis Register with a review of the literature. II. Outcome at three years. *Rheumatology.* 39: 939-949.

Hart FD. Presentation of rheumatoid arthritis and its relation to prognosis. 1977, *Br Med J.* 2(6087):621-4.

Hashizume M, Mihara M. 2011, The roles of interleukin-6 in the pathogenesis of rheumatoid arthritis. *Arthritis.* 765624.

Hassell AB, Davis MJ, Fowler PD, Clarke S, Fisher J, Shadforth MF, Jones PW, Dawes PT. 1993, The relationship between serial measures of disease activity and outcome in rheumatoid arthritis. *Q J Med.* 86: 601-7.

Hazes JM, Taylor P, Strand V, Purcaru O, Coteur G, Mease P. 2010, Physical function improvements and relief from fatigue and pain are associated with increased productivity at work and at home in rheumatoid arthritis patients treated with certolizumab pegol. *Rheumatology.* 49: 1900-10.

Heiberg T, Kvien TK. 2002, Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: pain has highest priority. *Arthritis Rheum.* 47: 391-7.

Heikkilä R, Aho K, Heliövaara M, Knekt P, Reunanen A, Aromaa A, Leino A, Palosuo

- T: 1998, Serum androgen-anabolic hormones and the risk of rheumatoid arthritis. *Ann Rheum Dis.* 57: 281-285.
- Hewlett S, Ambler N, Almeida C, Cliss A, Hammond A, Kitchen K, Knops B, Pope D, Spears M, Swinkels A, Pollock J. 2011, Self-management of fatigue in rheumatoid arthritis: a randomised controlled trial of group cognitive-behavioural therapy. *Ann Rheum Dis.* 70: 1060-7.
- Hewlett S, Hehir M, Kirwan JR. 2007, Measuring fatigue in rheumatoid arthritis: a systematic review of scales in use. *Arthritis Rheum.* 57: 429-39.
- Hill J, Bird HA, Hopkins R, Lawton C, Wright V. 1992, Survey of satisfaction with care in a rheumatology outpatient clinic. *Ann Rheum Dis.* 51: 195-7.
- Hodges B, Kuper A, Reeves S. 2008, Discourse analysis. *BMJ.* 337: a879.
- Hooper DC, Evans RG. 1989, Anti-proliferative action of murine alpha-fetoprotein on activated T-lymphocytes. *J Reprod Immunol.* 16:83-96.
- Houssien DA, McKenna SP, Scott DL. 1997, The Nottingham Health Profile as a measure of disease activity and outcome in rheumatoid arthritis. *Br J Rheumatol.* 36: 69-73.
- Hsieh HF, Shannon SE. 2005, Three approaches to qualitative content analysis. *Qualitative Health Research.* 15: 1277-88.
- Hurst NP, Ruta DA, Kind P. 1998, Comparison of the MOS short form-12 (SF12) health status questionnaire with the SF36 in patients with rheumatoid arthritis. *Br J Rheumatol.* 37: 862-9.
- Hurst NP, Kind P, Ruta D, Hunter M, Stubbings A. 1997, Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). *Br J Rheumatol.* 36: 551-9.
- Huskisson EC, Hart FD: 1972, Pain threshold and arthritis. *Br Med J.* 4: 193-5.
- Huskisson EC. 1974, Measurement of pain: *Lancet.* ii: 1127-31.
- Huyser BA, Parker JC, Thoreson R, Smarr KL, Johnson JC, Hoffman R. 1998, Predictors of subjective fatigue among individuals with rheumatoid arthritis. *Arthritis Rheum.* 41: 2230-7.
- Iaquinta ML, Larrabee JH. 2004, Phenomenological lived experience of patients with rheumatoid arthritis. *J Nurs Care Qual.* 19: 280-289.
- Inglis JJ, Nissim A, Lees DM, Hunt SP, Chernajovsky Y, Kidd BL. 2005, The differential contribution of tumour necrosis factor to thermal and mechanical hyperalgesia during chronic inflammation. *Arthritis Res Ther.* 7: R807-16.
- Irony-Tur-Sinai M, Grigoriadis N, Lourbopoulos A, Pinto-Maaravi F, Abramsky O, Brenner T. 2006, Amelioration of autoimmune neuroinflammation by recombinant human alpha-fetoprotein. *Exp Neurol.* 198:136-44.
- Jacobi CE, Boshuizen HC, Rupp I, Dinant HJ, van den Bos GA. 2004, Quality of rheumatoid arthritis care: the patient's perspective. *Int J Qual Health Care.* 16: 73-81.

- Jarupongprapa S, Ussavasodhi P, Katchamart W. 2012, Comparison of gastrointestinal adverse effects between cyclooxygenase-2 inhibitors and non-selective, non-steroidal anti-inflammatory drugs plus proton pump inhibitors: a systematic review and meta-analysis. *J Gastroenterol*. Dec 4. [Epub ahead of print]
- Jones PW, Ziade MF, Davis MJ, Dawes PT. 1993, An index of disease activity in rheumatoid arthritis. *Stat Med*. 12: 1171-81.
- Jump RL, Fifield J, Tennen H, Reisine S, Giuliano AJ. 2004, History of affective disorder and the experience of fatigue in rheumatoid arthritis. *Arthritis Rheum*. 51: 239-45.
- Jüni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. 2004, Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet*. 364(9450): 2021-9.
- Kapoor SR, Hider SL, Brownfield A, Matthey DL, Packham JC. 2011, Fibromyalgia in patients with rheumatoid arthritis: driven by depression or joint damage? *Clin Exp Rheumatol*. 29(6 Suppl 69):S88-91.
- Katz PP, Yelin EH. 1993, Prevalence and correlates of depressive symptoms among persons with rheumatoid arthritis. *J Rheumatol*. 20: 790-6.
- Kaye JJ. 1991, Radiographic methods of assessment (scoring) of rheumatic disease. *Rheum Dis Clin North Am*. 17(3):457-70.
- Kaye JJ, Nance EP Jr, Callahan LF, Carroll FE, Winfield AC, Earthman WJ, Phillips KA, Fuchs HA, Pincus T. 1987, Observer variation in quantitative assessment of rheumatoid arthritis Part II. A simplified scoring system. *Invest Radiol*. 1: 41-6.
- Kekow J, Moots R, Khandker R, Melin J, Freundlich B, Singh A. 2011, Improvements in patient-reported outcomes, symptoms of depression and anxiety, and their association with clinical remission among patients with moderate-to-severe active early rheumatoid arthritis. *Rheumatology*. 50: 401-9.
- Kelly MP, Field D. 1996, Medical sociology, chronic illness and the body. *Sociology of Health and Illness*. 18: 241-57.
- Kendall M, Murray SA, Carduff E, Worth A, Harris F, Lloyd A, Cavers D, Grant L, Boyd K, Sheikh A. 2009, Use of multiperspective qualitative interviews to understand patients' and carers' beliefs, experiences, and needs. *BMJ*. 339: b4122.
- Kennedy T, McCabe C, Struthers G, Sinclair H, Chakravaty K, Bax D, Shipley M, Abernethy R, Palferman T, Hull R; British Society for Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). 2005, BSR guidelines on standards of care for persons with rheumatoid arthritis. *Rheumatology*. 44: 553-6.
- Kerola AM, Kauppi MJ, Kerola T, Nieminen TV. 2012, How early in the course of rheumatoid arthritis does the excess cardiovascular risk appear? *Ann Rheum Dis*. 71: 1606-15.
- Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, Pazdur J, Bae SC, Palmer W, Zrubek J, Wiekowski M, Visvanathan S, Wu Z, Rahman MU. 2009, Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly

subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis.* 68: 789-96.

Kiely P, Walsh D, Williams R, Young A; 2011, Early Rheumatoid Arthritis Network. Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity--the early RA network (ERAN). *Rheumatology.* 50: 926-31.

Kingsley GH, Khoshaba B, Smith CM, Choy EH, Scott DL. 2005, Are clinical trials in rheumatoid arthritis generalizable to routine practice? A re-evaluation of trial entry criteria. *Rheumatology.* 44: 629-32.

Kinser AM, Sands WA, Stone MH. 2009, Reliability and validity of a pressure algometer. *J Strength Cond Res.* 23: 312-4.

Kirwan JR, Minnock P, Adebajo A, Bresnihan B, Choy E, de Wit M, Hazes M, Richards P, Saag K, Suarez-Almazor M, Wells G, Hewlett S. 2007, Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. *J Rheumatol.* 34: 1174-7.

Kjeken I, Dagfinrud H, Mowinckel P, Uhlig T, Kvien TK, Finset A. 2006, Rheumatology care: involvement in medical decisions, received information, satisfaction with care, and unmet health care needs in patients with rheumatoid arthritis and ankylosing spondylitis. *Arthritis Rheum.* 55: 394-401.

Klepinger LL. 1978, Paleopathologic evidence for the evolution of rheumatoid arthritis. *Am J Phys Anthropol.* 50: 119-22.

Kumar K, Daley E, Khattak F, Buckley CD, Raza K. 2010, The influence of ethnicity on the extent of, and reasons underlying, delay in general practitioner consultation in patients with RA. *Rheumatology.* 49: 1005-12.

Kunz S, Tegeder I, Coste O, Marian C, Pfenninger A, Corvey C, Karas M, Geisslinger G, Niederberger E. 2005, Comparative proteomic analysis of the rat spinal cord in inflammatory and neuropathic pain models. *Neurosci Lett.* 381: 289-93.

Landré-Beauvais AJ. 2001, The first description of rheumatoid arthritis. Unabridged text of the doctoral dissertation presented in 1800. *Joint Bone Spine.* 68: 130-43

Lansbury J, Haut DD. 1956, Quantitation of the manifestations of rheumatoid arthritis. 4. Area of joint surfaces as an index to total joint inflammation and deformity. *Am J Med Sci.* 232: 150-5.

Lansbury J. 1958, Numerical method of evaluating the status of rheumatoid arthritis. *Ann Rheum Dis.* 17: 101-7.

Larsen A. 1974, A radiological method for grading the severity of rheumatoid arthritis, Academic dissertation, University of Helsinki. Helsinki.

Larsen A. 1975, A radiological method for grading the severity of rheumatoid arthritis. *Scand J Rheumatol.* 4: 225-33

Larsen A, Dale K, Eek M. 1977, Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. *Acta Radiol Diagn (Stockh).* 18: 481-91.

Larsen A, Edgren J, Harju E, Laasonen L, Reitamo T. 1979, Interobserver variation in

the evaluation of radiologic changes of rheumatoid arthritis. *Scand J Rheumatol.* 8: 109-12.

Leandro MJ, Edwards JC, Cambridge G. 2002, Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion. *Ann Rheum Dis.* 61: 883-8.

Lee YC, Chibnik LB, Lu B, Wasan AD, Edwards RR, Fossel AH Helfgott SM, Solomon DH, Clauw DJ, Karlson EW. 2009, The relationship between disease activity, sleep, psychiatric distress and pain sensitivity in rheumatoid arthritis: a cross-sectional study. *Arthritis Res Ther.* 11: R160.

Lee YC, Cui J, Lu B, Frits ML, Iannaccone CK, Shadick NA, Weinblatt ME, Solomon DH. 2011, Pain persists in DAS28 rheumatoid arthritis remission but not in ACR/EULAR remission: a longitudinal observational study. *Arthritis Res Ther.* 13: R83

Lee YC. 2013, Effect and treatment of chronic pain in inflammatory arthritis. *Curr Rheumatol Rep.* 15: 300.

Leeb BF, Andel I, Sautner J, Nothnagl T, Rintelen B. 2004, The DAS28 in rheumatoid arthritis and fibromyalgia patients. *Rheumatology.* 43: 1504-7.

Lempp H, Scott D, Kingsley G. 2006, Patients' views on the quality of health care for rheumatoid arthritis. *Rheumatology.* 45: 1522-1528.

Lempp H, Scott D, Kingsley G. 2006, The personal impact of rheumatoid arthritis on patients' identity: a qualitative study. *Chronic Illn.* 2: 109-20.12.

MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, Silman AJ. 2000, Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum.* 43: 30-7.

Maini RN, Taylor PC, Szechinski J, Pavelka K, Bröhl J, Balint G, Emery P, Raemen F, Petersen J, Smolen J, Thomson D, Kishimoto T; CHARISMA Study Group. 2006, Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum.* 54: 2817-29.

Mäkinen H, Hannonen P. 2009, How to assess patients with rheumatoid arthritis and concomitant fibromyalgia? *J Rheumatol.* 36: 9-11.

Mallya RK, Mace BE. 1981, The assessment of disease activity in rheumatoid arthritis using a multivariate analysis. *Rheumatol Rehabil.* 20: 14-7.

Margaretten M, Yelin E, Imboden J, Graf J, Barton J, Katz P, Julian L. 2009, Predictors of depression in a multiethnic cohort of patients with rheumatoid arthritis. *Arthritis Rheum.* 61(11):1586-91.

Mathieux R, Marotte H, Battistini L, Sarrazin A, Berthier M, Miossec P. 2009, Early occupational therapy programme increases hand grip strength at 3 months: results from a randomised, blind, controlled study in early rheumatoid arthritis. *Ann Rheum Dis.* 68: 400-3.

McHorney CA, Ware JE Jr, Raczek AE. 1993, The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care.* 31: 247-63.

- Meenan RF, Gertman PM, Mason JH. 1980, Measuring health status in arthritis. The arthritis impact measurement scales. *Arthritis Rheum.* 23: 146-52.
- Melzack R. 1983, The McGill Pain Questionnaire. In Melzack R (ed). *Pain Measurement and Assessment*. New York: Raven press. pp 41-47.
- Melzack R. 1987, The short-form McGill pain questionnaire. *Pain.* 30: 191-197.
- Meyer O, de Bandt M, Berthelot JM, Cantagrel A, Combe B, Fautrel B, Flipo RM, Lioté F, Maillefert JF, Saraux A, Wendling D, Guillemin F, Le Loët X; Working Group for Therapeutic Strategies for Rheumatoid Arthritis. 2007, Clinical practice format for choosing a second-line disease modifying anti-rheumatic drug in early rheumatoid arthritis after failure of 6 months' first-line DMARD therapy. *Joint Bone Spine.* 74: 73-8.
- Morel J, Combe B. 2005, How to predict prognosis in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol.* 19: 137-46.
- National Audit Office. (NAO) 2009, Services for people with rheumatoid arthritis. Report by the comptroller and auditor general, HC 823 session 2008–2009. National Audit Office. 6191539 07/09 65536 ed. London: HMSO.
- National Institute of Clinical Excellence Guidance (NICE) 2010, Abatacept: <http://guidance.nice.org.uk/TA195> and Tocilizumab: <http://guidance.nice.org.uk/TA198>
- National Institute of Clinical Excellence (NICE) 2007 Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. National Institute for Health and Clinical Excellence. <http://www.nice.org.uk/TA130>
- National Institute of Clinical Excellence Guidance (NICE) 2010, Certolizumab: <http://guidance.nice.org.uk/TA186>
- National Institute of Clinical Excellence Guidance (NICE) 2011, Golimumab: <http://guidance.nice.org.uk/TA225>
- National Institute of Clinical Excellence (NICE) 2009, Rheumatoid arthritis: the management of rheumatoid arthritis in adults. National Institute for Health and Clinical Excellence. <http://www.nice.org.uk/Guidance/CG79>
- National Institute of Clinical Excellence (NICE) 2010, Guidance Technology Appraisal 195 (TA195). Rheumatoid arthritis – drugs for treatment after failure of a TNF inhibitor. www.nice.org.uk/ta195
- Neame R, Hammond A, Deighton C. 2005, Need for information and for involvement in decision making among patients with rheumatoid arthritis: a questionnaire survey. *Arthritis & Rheumatism.* 53: 249–55.
- Neugebauer V, Schaible HG. 1990, Evidence for a central component in the sensitization of spinal neurons with joint input during development of acute arthritis in cat's knee. *J Neurophysiol.* 64: 299-311.
- Nikolaus S, Bode C, Taal E, Laar MA. 2012, Which Dimensions of Fatigue Should be Measured in Patients with Rheumatoid Arthritis? A Delphi Study. *Musculoskeletal Care* 10: 13-7.
- O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ, Garwood V,

- Maloley P, Klassen LW, Wees S, Klein H, Moore GF. 1996, Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med.* 334: 1287-91.
- Ostensen M, Villiger PM. 2002, Immunology of pregnancy—pregnancy as a remission inducing agent in rheumatoid arthritis. *Transpl Immunol* 9:155–60.
- Otter SJ, Lucas K, Springett K, Moore A, Davies K, Young A, Walker-Bone K. 2012, Identifying Patient-Reported Outcomes in Rheumatoid Arthritis: The Impact of Foot Symptoms on Self-Perceived Quality of Life. *Musculoskeletal Care.* 10: 65-75
- Otter SJ, Lucas K, Springett K, Moore A, Davies K, Young A, Walker-Bone K. 2011, Comparison of foot pain and foot care among rheumatoid arthritis patients taking and not taking anti-TNF α therapy: an epidemiological study. *Rheumatol Int.* 31: 1515-9.
- Ouédraogo DD, Singbo J, Diallo O, Sawadogo SA, Tiéno H, Drabo YJ. 2011, Rheumatoid arthritis in Burkina Faso: clinical and serological profiles. *Clin Rheumatol.* 30: 1617-21.
- Overland J, Mira M, Yue D. 2001, Differential shared care for diabetes: does it provide the optimal partition between primary and specialist care? *Diabetic Medicine.* 18: 554-7.
- Pairet M, Engelhardt G. 1996, Distinct isoforms (COX-1 and COX-2) of cyclooxygenase: possible physiological and therapeutic implications. *Fundam Clin Pharmacol.* 10: 1-17.
- Picavet HS, Hoeymans N. 2004, Health related quality of life in multiple musculoskeletal diseases: SF-36 and EQ-5D in the DMC3 study. *Ann Rheum Dis.* 63: 723-9.
- Pinals RS, Masi AT, Larsen RA. 1981, Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum.* 24: 1308-15.
- Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. 1983, Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum.* 26: 1346-53.
- Pincus T, Swearingen C, Wolfe F. 1999, Toward a multidimensional Health Assessment Questionnaire (MDHAQ): assessment of advanced activities of daily living and psychological status in the patient-friendly health assessment questionnaire format. *Arthritis Rheum.* 42: 2220-30.
- Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. 2006, Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology.* 45: 885-9.
- Pollard LC, Kingsley GH, Choy EH, Scott DL. 2010, Fibromyalgic rheumatoid arthritis and disease assessment. *Rheumatology.* 49: 924-8.
- Pollard LC, Murray J, Moody M, Stewart EJ, Choy EH. 2007, A randomised, double-blind, placebo-controlled trial of a recombinant version of human alpha-fetoprotein (MM-093) in patients with active rheumatoid arthritis. *Ann Rheum Dis.* 66: 687-9.
- Pollard LC. 2007, Inhibiting costimulatory activation of T cells: a viable treatment option for rheumatoid arthritis? *Drugs.* 67: 1-9.

- Pollock J, McFarlane SM, Connell MC, Zehavi U, Vandenabeele P, MacEwan DJ, Scott RH. 2002, TNF-alpha receptors simultaneously activate Ca²⁺ mobilisation and stress kinases in cultured sensory neurones. *Neuropharmacology*. 42: 93-106.
- Polsky D, Doshi JA, Marcus S, Oslin D, Rothbard A, Thomas N, Thompson CL. 2005, Long-term risk for depressive symptoms after a medical diagnosis. *Arch Intern Med*. 165: 1260-6.
- Potter, J. 1997, Discourse analysis as a way of analysing naturally occurring talk. in: *Qualitative Research. Theory, Method and Practice*. D. Silverman, ed. Sage Publications: London, pp. 144-160.
- Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. 1995, Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum*. 38: 44-8.
- Ranzolin A, Brenol JC, Bredemeier M, Guarienti J, Rizzatti M, Feldman D, Xavier RM. 2009, Association of concomitant fibromyalgia with worse disease activity score in 28 joints, health assessment questionnaire, and short form 36 scores in patients with rheumatoid arthritis. *Arthritis Rheum*. 61: 794-800.
- Rasker JJ, Cosh JA. 1981, Cause and age at death in a prospective study of 100 patients with rheumatoid arthritis. *Ann Rheum Dis*. 40: 115-20.
- Ravindran V, Seah MA, Elias DA, Choy EH, Scott DL, Gordon PA. 2008, Clinical and radiological features of rheumatoid arthritis in British black Africans. *Clin Rheumatol*. 27: 97-100.
- Raza K, Stack R, Kumar K, Filer A, Detert J, Bastian H, Burmester GR, Sidiropoulos P, Kteniadaki E, Repa A, Saxne T, Turesson C, Mann H, Vencovsky J, Catrina A, Chatzidionysiou A, Hensvold A, Rantapää-Dahlqvist S, Binder A, Machold K, Kwiakowska B, Ciurea A, Tamborrini G, Kyburz D, Buckley CD. 2011, Delays in assessment of patients with rheumatoid arthritis: variations across Europe. *Ann Rheum Dis*. 70: 1822-5.
- Reese EP. 1958, Arthritis; the use of physical therapy as an aspect of management. *Calif Med*. 89(3):204-9.
- Riemsma RP, Rasker JJ, Taal E, Griep EN, Wouters JM, Wiegman O. 1998, Fatigue in rheumatoid arthritis: the role of self-efficacy and problematic social support. *Br J Rheumatol*. 37: 1042-6.
- Ritchie DM, Boyle JA, McInnes JM, Jasani MK, Dalakos TG, Grieveson P, Buchanan WW. 1968, Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q J Med*. 37: 393-406.
- Robinson PC, Taylor WJ. 2010, Time to treatment in rheumatoid arthritis: factors associated with time to treatment initiation and urgent triage assessment of general practitioner referrals. *J Clin Rheumatol*. 16: 267-73.
- Rupp I, Boshuizen H, Jacobi CE, Dinant HJ, van den Bos GA. 2004, Impact of fatigue on health-related quality of life in rheumatoid arthritis. *Arthritis Care Res*. 51: 578-85.

- Rupp I, Boshuizen HC, Dinant HJ, Jacobi CE, van den Bos GA. 2006, Disability and health-related quality of life among patients with rheumatoid arthritis: association with radiographic joint damage, disease activity, pain, and depressive symptoms *Scand J Rheumatol.* 35: 175-81.
- Ruta DA, Hurst NP, Kind P, Hunter M, Stubbings A. 1998, Measuring health status in British patients with rheumatoid arthritis: reliability, validity and responsiveness of the short form 36-item health survey (SF-36). *Br J Rheumatol.* 37: 425-36.
- Sakthong P. 2008, Measurement of clinical-effect: utility. *J Med Assoc Thai.* 91 Suppl 2:S43-52.
- Schaible HG, Grubb BD. 1993, Afferent and spinal mechanisms of joint pain. *Pain.* 55: 5-54.
- Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, van Venrooij WJ. 2000, The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum.* 43: 155-63.
- Scott DL, Garrood T. 2000, Quality of life measures: use and abuse. *Baillieres Best Pract Res Clin Rheumatol.* 14: 663-87.
- Scott DL, Houssien DA, Laasonen L. 1995, Proposed modification to Larsen's scoring methods for hand and wrist radiographs. *Br J Rheumatol.* 34: 56.
- Scott DL, Smith C, Kingsley G. 2005, What are the consequences of early rheumatoid arthritis for the individual? *Best Pract Res Clin Rheumatol.* 19: 117-36.
- Scott DL, Steer S. 2007, The course of established rheumatoid arthritis. *Best Pract Res Clin Rheumatol.* 21: 943-67.
- Scott PA, Kingsley GH, Smith CM, Choy EH, Scott DL. 2007, Non-steroidal anti-inflammatory drugs and myocardial infarctions: comparative systematic review of evidence from observational studies and randomised controlled trials. *Ann Rheum Dis.* 66: 1296-304.
- Scottish Intercollegiate Guidelines Network. 2000, Management of early rheumatoid arthritis. SIGN Publication No. 48. Royal College of Physicians. www.sign.ac.uk/pdf/qrg48.pdf.
- Seale, C. & Kelly, M. 1998, Coding and analysing data; in: *Researching Society and Culture*, C. Seale, ed. Sage Publications: London, pp. 146-163.
- Seale, C. 1999, *The Quality of Qualitative Research. Introducing Qualitative Methods.* Sage Publications: London. Chapter 6 & 8.
- Sharp JT, Lidsky MD, Collins LC, Moreland J. 1971, Methods of scoring the progression of radiologic changes in rheumatoid arthritis. Correlation of radiologic, clinical and laboratory abnormalities. *Arthritis Rheum.* 14: 706-20.
- Sharp JT, Young DY, Bluhm GB, Brook A, Brower AC, Corbett M, Decker JL, Genant HK, Gofton JP, Goodman N. 1985, How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? *Arthritis Rheum.* 28: 1326-35.

- Shiozawa S, Tsumiyama K, Yoshida K, Hashiramoto A. 2011, Pathogenesis of joint destruction in rheumatoid arthritis. *Arch Immunol Ther Exp (Warsz)*. 59: 89-95.
- Sierakowski S, Cutolo M. 2011, Morning symptoms in rheumatoid arthritis: a defining characteristic and marker of active disease. *Scand J Rheumatol Suppl*. 125:1-5.
- Masi AT. 1983, Articular patterns in the early course of rheumatoid arthritis. *Am J Med* 75: 16-26.
- Silman AJ, Hochberg MC. 2001, Rheumatoid arthritis. In *Epidemiology of the Rheumatic Diseases* (Edited by: Edited by AJ Silman, MC Hochberg). Oxford: Oxford University Press; pp. 31-71.
- Silman AJ, Pearson JE. 2002, Epidemiology and genetics of rheumatoid arthritis. *Arthritis Res*. 4 Suppl 3: S265-72.
- Silverman, D. 1993, *Interpreting Qualitative Data: Methods for Analysing Talk, Text and Interaction*. Sage Publications: London.
- Sivas F, Ercin O, Tanyolac O, Barca N, Aydog S, Ozoran K. 2004, The Nottingham Health Profile in rheumatoid arthritis: correlation with other health status measurements and clinical variables. *Rheumatol Int*. 24: 203-6.
- Smolen JS. 1992, The work of the EULAR Standing Committee on International Clinical Studies Including Therapeutic Trials (ESCISIT). *Br J Rheumatol*. 31: 219-20.
- Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, Kirkpatrick J. 1995, Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. *Arthritis Rheum*. 38: 38-43.
- Smolen JS, Han C, van der Heijde D, Emery P, Bathon JM, Keystone E, Kalden JR, Schiff M, Bala M, Baker D, Han J, Maini RN, St Clair EW. 2006, Infliximab treatment maintains employability in patients with early rheumatoid arthritis. *Arthritis Rheum*. 54: 716-22.
- Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, Gorter S, Knevel R, Nam J, Schoels M, Aletaha D, Buch M, Gossec L, Huizinga T, Bijlsma JW, Burmester G, Combe B, Cutolo M, Gabay C, Gomez-Reino J, Kouloumas M, Kvien TK, Martin-Mola E, McInnes I, Pavelka K, van Riel P, Scholte M, Scott DL, Sokka T, Valesini G, van Vollenhoven R, Winthrop KL, Wong J, Zink A, van der Heijde D. 2010, EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis*. 69: 964-75.
- Soderlin MK, Kautiainen H, Skogh T, Leirisalo-Repo M. 2004, Quality of life and economic burden of illness in very early arthritis. A population based study in southern Sweden. *J Rheumatol*. 31: 1717-22.
- Sokka T, Kankainen A, Hannonen P. 2000, Scores for functional disability in patients with rheumatoid arthritis are correlated at higher levels with pain scores than with radiographic scores. *Arthritis Rheum*. 43: 386-9.
- Sokka T, Kautiainen H. 2005, Further development of a physical function scale on a Multidimensional Health Assessment Questionnaire for standard care of patients with

rheumatic diseases. *J Rheumatol.* 32: 1432-9.

Spector TD, Perry LA, Tubb G, Silman AJ, Huskisson EC. 1988, Low free testosterone levels in rheumatoid arthritis. *Ann Rheum Dis.* 47: 65-8.

Spector TD, Roman E, Silman AJ. 1989, A UK case-control study on the effect of parity and the oral contraceptive pill on the development of rheumatoid arthritis. *Br J Rheumatol.* 28 Suppl 1:32; discussion 42-5.

Standards of Care for people with Inflammatory Arthritis. 2004, London: Arthritis and Musculoskeletal Alliance.

Stavem K, Lossius MI, Kvien TK, Guldvog B. 2000, The health-related quality of life of patients with epilepsy compared with angina pectoris, rheumatoid arthritis, asthma and chronic obstructive pulmonary disease. *Qual Life Res.* 9: 865-71.

Stein KD, Martin SC, Hann DM, Jacobsen PB. 1998, A multidimensional measure of fatigue for use with cancer patients. *Cancer Pract.* 6: 143-52.

Steward K, Land M. 2009, Perceptions of patients and professionals on rheumatoid arthritis. London: King's Fund.

Stewart MW, Palmer DG, Knight RG. 1990, A self-report articular index measure of arthritic activity: investigations of reliability, validity and sensitivity. *J Rheumatol.* Aug; 17: 1011-5.

Storey GD. 2001, Alfred Baring Garrod (1819-1907). *Rheumatology (Oxford).* 40: 1189-90.

Strand V, Scott DL, Emery P, Kalden JR, Smolen JS, Cannon GW, Tugwell P, Crawford B; Leflunomide Rheumatoid Arthritis Investigators Groups. 2005, Physical function and health related quality of life: analysis of 2-year data from randomized, controlled studies of leflunomide, sulfasalazine, or methotrexate in patients with active rheumatoid arthritis. *J Rheumatol.* 32: 590-601.

Sudore RL, Karter AJ, Huang ES, Moffet HH, Laiteerapong N, Schenker Y, Adams A, Whitmer RA, Liu JY, Miao Y, John PM, Schillinger D. 2012, Symptom burden of adults with type 2 diabetes across the disease course: diabetes & aging study. *J Gen Intern Med.* 27(12):1674-81.

Suter LG, Fraenkel L, Holmboe ES. 2006, What factors account for referral delays for patients with suspected rheumatoid arthritis? *Arthritis Rheum.* 55: 300-5.

Suurmeijer TP, Waltz M, Moum T, Guillemin F, van Sonderen FL, Briancon S, Sanderman R, van den Heuvel WJ. 2001, Quality of life profiles in the first years of rheumatoid arthritis: results from the EURIDISS longitudinal study. *Arthritis Rheum.* 45: 111-21.

Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL. 2005, The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis. *Health Technol Assess.* 9: 1-78.

Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, Scott D, Silman A. 2002, The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new

century. *Rheumatology*. 41: 793-800.

Symmons DP, Hassell AB, Gunatillaka KA, Jones PJ, Schollum J, Dawes PT. 1995, Development and preliminary assessment of a simple measure of overall status in rheumatoid arthritis (OSRA) for routine clinical use. *QJM*. 88: 429-37.

Syversen SW, Gaarder PI, Goll GL, Ødegård S, Haavardsholm EA, Mowinckel P, van der Heijde D, Landewé R, Kvien TK. 2008, High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. *Ann Rheum Dis*. 67:212-7.

Tack B. 1990, Self-reported fatigue in rheumatoid arthritis: a pilot study. *Arthritis Care Res*. 3: 154-7.

Tavakol M, Dennick R. 2011, Making sense of Cronbach's alpha. *International Journal of Medical Education*. 2:53-55.

Tavares R, Pope JE, Tremblay JL, Thorne C, Bykerk VP, Lazovskis J, Blocka KL, Bell MJ, Lacaille D, Hitchon CA, Fitzgerald AA, Fidler WK, Bookman AA, Henderson JM, Mosher DP, Sholter DE, Khraishi M, Haraoui B, Chen H, Li X, Laupacis A, Boire G, Tomlinson G, Bombardier C. 2011, Early management of newly diagnosed rheumatoid arthritis by Canadian rheumatologists: a National, Multicenter, Retrospective cohort. *J Rheumatol*. 38: 2342-5.

Telleria-Diaz A, Schmidt M, Kreusch S, Neubert AK, Schache F, Vazquez E, Vanegas H, Schaible HG, Ebersberger A. 2010, Spinal antinociceptive effects of cyclooxygenase inhibition during inflammation: Involvement of prostaglandins and endocannabinoids. *Pain*. 148: 26-35.

Thompson PW, Silman AJ, Kirwan JR, Currey HL. 1987, Articular indices of joint inflammation in rheumatoid arthritis. Correlation with the acute-phase response. *Arthritis Rheum*. 30: 618-23.

Tijhuis GJ, Kooiman KG, Zwinderman AH, Hazes JM, Breedveld FC, Vliet Vlieland TP. 2003, Validation of a novel satisfaction questionnaire for patients with rheumatoid arthritis receiving outpatient clinical nurse specialist care, inpatient care, or day patient team care. *Arthritis and Rheumatism*. 49: 193-9.

Tijhuis GJ, Zwinderman AH, Hazes JM, Breedveld FC, Vlieland PM. 2003, Two- year follow-up of a randomized controlled trial of a clinical nurse specialist intervention, inpatient, and day patient team care in rheumatoid arthritis. *J Adv Nurs*. 41: 34-43.

Toda Y, Minamikawa Y, Akagi S, Sugano H, Mori Y, Nishimura H, Arita S, Sugino Y, Ogawa R. 1994, Rheumatoid-susceptible alleles of HLA-DRB1 are genetically recessive to non-susceptible alleles in the progression of bone destruction in the wrists and fingers of patients with RA. *Ann Rheum Dis*. 53: 587-92.

Ton E, Bakker MF, Verstappen SM, Ter Borg EJ, van Albada-Kuipers IA, Schenk Y, van der Veen MJ, Bijlsma JW, Jacobs JW; Utrecht Rheumatoid Arthritis Cohort Study Group. 2012, Look beyond the disease activity score of 28 joints (DAS28): tender points influence the DAS28 in patients with rheumatoid arthritis. *J Rheumatol*. 39: 22-7.

- Tonkiss, F. 1998, Analysing discourse. in: *Researching Society and Culture.*, C. Seale, ed. Sage Publications: London, pp. 245-260.
- Tugwell P, Boers M. 1993, Developing consensus on preliminary core efficacy endpoints for rheumatoid arthritis clinical trials. OMERACT Committee. *J Rheumatol.* 20: 555-6.
- Tugwell P, Boers M. 1992, OMERACT conference on outcome measures in rheumatoid arthritis clinical trials: introduction. *J Rheumatol.* 20: 528-30.
- Turesson C, Jacobsson L, Bergström U. 1999, Extra-articular rheumatoid arthritis: prevalence and mortality. *Rheumatology.* 38: 668-74.
- Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. 2002, Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. *J Rheumatol.* 29: 62-7.
- Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. 2003, Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis.* 62: 722-7.
- Uhlig T. 2011, The history of rheumatoid arthritis. *European Musculoskeletal Review.* 6: 145-7
- Ulus Y, Akyol Y, Tander B, Durmus D, Bilgici A, Kuru O. 2011, Sleep quality in fibromyalgia and rheumatoid arthritis: associations with pain, fatigue, depression, and disease activity. *Clin Exp Rheumatol.* 29: S92-6.
- Uutela T, Hakala M, Kautiainen H. 2003, Validity of the Nottingham Health Profile in a Finnish out-patient population with rheumatoid arthritis. *Rheumatology.* 42: 841-5.
- van der Heijde D. 1999, How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol.* 26: 743-5.
- van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. 1993, Development of a disease activity score based on judgment in clinical practice by rheumatologists. *J Rheumatol.* 20: 579-81.
- van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, van Rijswijk MH, van de Putte LB. 1990, Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis.* 49: 916-20.
- Van Dyke MM, Parker JC, Smarr KL, Hewett JE, Johnson GE, Slaughter JR, Walker SE. 2004, Anxiety in rheumatoid arthritis. *Arthritis Rheum.* 51: 408-12.
- Van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. 1996, Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis: comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism criteria. *Arthritis Rheum.* 39: 34-40.
- van Hoogmoed D, Fransen J, Bleijenberg G, van Riel P. 2010, Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. *Rheumatology.* 49: 1294-302.

- van Hulst LT, Kievit W, van Bommel R, van Riel PL, Fraenkel L. 2011, Rheumatoid arthritis patients and rheumatologists approach the decision to escalate care differently: results of a maximum difference scaling experiment. *Arthritis Care Res.* 63: 1407-14.
- van Kessel K, Moss-Morris R, Willoughby E, Chalder T, Johnson MH, Robinson E. 2008, A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue. *Psychosom Med.* 70: 205-13.
- van Leeuwen MA, van der Heijde DM, van Rijswijk MH, Houtman PM, van Riel PL, van de Putte LB, Limburg PC. 1994, Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. *J Rheumatol.* 21: 425-9.
- van Venrooij WJ, Hazes JM, Visser H. 2002, Anticitrullinated protein/peptide antibody and its role in the diagnosis and prognosis of early rheumatoid arthritis. *Neth J Med.* 60: 383-8.
- van Vollenhoven RF, Askling J. 2005, Rheumatoid arthritis registries in Sweden. *Clin Exp Rheumatol.* 5 (Suppl 39): S195-200.
- van Zeben D, Hazes JM, Zwinderman AH, Cats A, van der Voort EA, Breedveld FC. 1992, Clinical significance of rheumatoid factors in early rheumatoid arthritis: results of a follow up study. *Ann Rheum Dis.* 51: 1029-35.
- Verhoeven AC, Boers M, Tugwell P. 1998, Combination therapy in rheumatoid arthritis: updated systematic review. *Br J Rheumatol.* 37: 612-9.
- Verstappen SM, McCoy MJ, Roberts C, Dale NE, Hassell AB, Symmons DP; STIVEA investigators. 2010, Beneficial effects of a 3-week course of intramuscular glucocorticoid injections in patients with very early inflammatory polyarthritis: results of the STIVEA trial. *Ann Rheum Dis.* 69: 503-9
- Ward V, Hill J, Hale C, Bird H, Quinn H, Thorpe R. 2007, Patient priorities of care in rheumatology outpatient clinics: a qualitative study. *Musculoskeletal Care.* 5(4):216-28.
- Ware JE Jr, Sherbourne CD. 1992, The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 30(6):473-83.
- Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, Teoh LA, Fischkoff SA, Chartash EK. 2003, Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* 48: 35-45.
- Welsing PM, Fransen J, van Riel PL. 2005, Is the disease course of rheumatoid arthritis becoming milder? Time trends since 1985 in an inception cohort of early rheumatoid arthritis. *Arthritis Rheum.* 52: 2616-24.
- West E, Jonsson SW. 2005, Health-related quality of life in rheumatoid arthritis in Northern Sweden: a comparison between patients with early RA, patients with medium-term disease and controls, using SF-36. *Clin Rheumatol.* 24: 117-22.
- Weyand CM, Hicok KC, Conn DL, Goronzy JJ. 1992, The influence of HLA-DRB1 genes on disease severity in rheumatoid arthritis. *Ann Intern Med.* 117: 801-6.

- White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M. 2011, PACE trial management group. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet*. 377: 823-36.
- Williams AE, Nester CJ, Ravey MI. 2007, Rheumatoid arthritis patients' experiences of wearing therapeutic footwear – A qualitative investigation. *BMC Musculoskeletal Disorders*. 8:104.
- Wilske KR, Healey LA. 1989, Remodeling the pyramid--a concept whose time has come. *J Rheumatol*. 16: 565-7.
- Winchester RJ. 1981, Genetic aspects of rheumatoid arthritis. *Springer Semin Immunopathol*. 4: 89-102.
- Wolfe F, Cathey MA, Kleinheksel SM. 1984, Fibrositis (Fibromyalgia) in rheumatoid arthritis. *J Rheumatol*. 11: 814-8.
- Wolfe F, Cathey MA. 1983, Prevalence of primary and secondary fibrositis. *J Rheumatol*. 10(6):965-8.
- Wolfe F, Cathey MA, Roberts FK. 1991, The latex test revisited. Rheumatoid factor testing in 8,287 rheumatic disease patients. *Arthritis Rheum*. 34(8):951-60.
- Wolfe F, Hawley DJ, Wilson K. 1996, The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol*. 23: 1407-17
- Wolfe F, Michaud K. 2007, Resistance of rheumatoid arthritis patients to changing therapy: discordance between disease activity and patients' treatment choices. *Arthritis & Rheumatism*. 56: 2135–2142.
- Wolfe F, Michaud K, Pincus T. 2004, Development and validation of the health assessment questionnaire II: a revised version of the health assessment questionnaire. *Arthritis Rheum*. 50: 3296-305.
- Wolfe F, Michaud K. 2004, Fatigue, rheumatoid arthritis, and anti-tumor necrosis factor therapy: an investigation in 24,831 patients. *J Rheumatol*. 31: 2115-20.
- Wolfe F, Michaud K. 2009, Outcome and Predictor Relationships in Fibromyalgia and Rheumatoid Arthritis: Evidence Concerning the Continuum versus Discrete Disorder Hypothesis. *J Rheumatol*. 36: 831-6.
- Wolfe F, Michaud K. 2005, Preliminary evaluation of a visual analog function scale for use in rheumatoid arthritis. *J Rheumatol*. 32: 1261-6.
- Wolfe F, Michaud K. 2004, Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize RA patients with fibromyalgia. *J Rheumatol*. 31: 695-700.
- Wolfe F, Petri M, Alarcón GS, Goldman J, Chakravarty EF, Katz RS, Karlson EW. 2009, Fibromyalgia, Systemic Lupus Erythematosus (SLE), and Evaluation of SLE Activity. *J Rheumatol*. 36: 82-8.

- Wolfe F, Pincus T, Fries JF. 2001, Usefulness of the HAQ in the clinic. *Ann Rheum Dis.* 60: 811.
- Wolfe F. 2000, A reappraisal of HAQ disability in rheumatoid arthritis. *Arthritis Rheum.* 43: 2751–61.
- Wolfe F. 2004, Fatigue assessments in rheumatoid arthritis: comparative performance of visual analog scales and longer fatigue questionnaires in 7760 patients. *J Rheumatol.* 31: 1896-902.
- Wolfe F. 2009, Fibromyalgianess. *Arthritis Rheum.* 61: 715-6.
- Wolfe F. 2001, Which HAQ is best? A comparison of the HAQ, MHAQ and RA-HAQ, a difficult 8 item HAQ (DHAQ), and a rescored 20 item HAQ (HAQ20): analyses in 2,491 rheumatoid arthritis patients following leflunomide initiation. *J Rheumatol.* 28: 982-9.
- Wolfe F, Häuser W, Hassett AL, Katz RS, Walitt BT. 2011, The development of fibromyalgia--I: examination of rates and predictors in patients with rheumatoid arthritis (RA). *Pain.* 152(2):291-9.
- Woodburn J, Barker S, Helliwell PS. 2002, A randomized controlled trial of foot orthoses in rheumatoid arthritis. *J Rheumatol.* 29: 1377-83.
- Woolf CJ, Allchorne A, Safieh-Garabedian B, Poole S. 1997, Cytokines, nerve growth factor and inflammatory hyperalgesia: the contribution of tumour necrosis factor α . *Br J Pharmacol.* 121: 417-24.
- Worth A, Irshad T, Bhopal R, Brown D, Lawton J, Grant E, Murray S, Kendall M, Adam J, Gardee R, Sheikh A. 2009, Vulnerability and access to care for South Asian Sikh and Muslim patients with life limiting illness in Scotland: prospective longitudinal qualitative study. *BMJ.* 338: b183.
- Wylde V, Palmer S, Learmonth ID, Dieppe P. 2011, Test-retest reliability of Quantitative Sensory Testing in knee osteoarthritis and healthy participants. *Osteoarthritis Cartilage.* 19: 655-8.
- Yamout B, Issa Z, Herlopian A, El Bejjani M, Khalifa A, Ghadieh AS, Habib RH. 2013, Predictors of quality of life among multiple sclerosis patients: a comprehensive analysis. *Eur J Neurol.* In press
- Zautra AJ, Burleson MH, Matt KS, Roth S, Burrows L. 1994 Interpersonal stress, depression, and disease activity in rheumatoid arthritis and osteoarthritis patients. *Health Psychol.* 13: 139-48.
- Zhang W, Anis AH. 2011 The economic burden of rheumatoid arthritis: beyond health care costs. *Clin Rheumatol.* 30 Suppl 1 :S25-32.
- Zigmond AS, Snaith RP. 1983 The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica.* 67: 361-370.

APPENDICES

Appendix 1: Patients focus group consent form

CONSENT FORM FOR PARTICIPATION IN RESEARCH PROJECTS AND CLINICAL TRIALS

Principal Investigator: Dr L. Pollard BSc MSc MRCP
King's College Hospital
Denmark Hill
London
SE5 9RS

**Title of Project: Standards Of Care For People With Inflammatory Arthritis:
Establishing A Local Framework To Deliver National Standards - Defining
Patients Needs.**

Name of Researcher: Dr L. Pollard BSc MSc MRCP

Please initial box

- | | |
|---|--------------------------|
| 1. I confirm that I have read and understand the information sheet dated July 17 th , 2006 (version 1) for the above study and have had the opportunity to ask questions without my medical care or legal rights being affected. | <input type="checkbox"/> |
| 2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, | <input type="checkbox"/> |
| 3. I understand that sections of any of my medical notes may be looked at by responsible individuals from King's College Hospital, and/or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. | <input type="checkbox"/> |
| 4. I agree to take part in the above study. | <input type="checkbox"/> |

Name of Patient

Date

Signature

Researcher

Date

Signature

Appendix 2: Patients focus group interview schedule

INTERVIEW SCHEDULE (Patients)

There are three main themes to be discussed in the focus group, firstly what information you feel should be provided about your illness and its management, secondly how you access medical services and finally what assessments you feel should be done in the outpatient clinic

At the end I would welcome any further information you may feel is relevant to your experience in the outpatient department, including your thoughts on taking part in the study. The focus groups will last for approximately one hour but can go on longer if needed. The discussion will be recorded on tape and can be paused at any time. If you provide any information you do not wish to have recorded, the tape recorder can be stopped at any time and restarted at your request.

Information Needs

1. How do you get information about your illness?
 - eg by whom
 - eg via internet/leaflets
 - eg patient groups
2. What information do you need to help you manage your own illness?
 - eg staying active
 - eg identifying symptoms and signs of inflammatory arthritis
 - eg managing pain
 - eg information on new drugs
 - eg help back to work
 - eg Benefits available
3. How would you like this information to be delivered?
 - eg website/leaflet
4. What type of information would you like on a website?
 - eg links to benefit agencies/updates on new treatments/advice on self-management

Access to Care

1. In your opinion who should decide when and how often you attend outpatients?
 - eg how often do you think you should be seen
 -
2. How important is continuity of care to you?
 - eg Do you usually see the same doctor? Is this important to you?
 -
3. What do you think is the role of your rheumatologist in your care?

4. What do you think is the role of your GP in your care?
 eg who do you think should monitor your other medical problems
 such as blood pressure, cholesterol etc.
 - eg where should you have your blood monitoring done?
5. How to you access care during a flare of your arthritis?
 - eg how easy is it to be seen at GP/rheumatology outpatients
 - eg telephone hotlines.
6. What other healthcare professionals have you seen about you arthritis?
 - eg hand therapists/OT/physio/podiatry
 - how important is it to see them
 - how easy is it to access them?

Outpatient Assessment

1. What questions are you currently asked when you attend the outpatient department?
2. What questions do you feel should be asked?
 a. eg fatigue, pain, sleep
3. What examinations do you expect to be carried out in your outpatient appointment?
 eg joint examination
 eg check feet
 eg blood pressure
 eg any other examinations which you feel are important

Appendix 3: Health professionals focus group consent form**CONSENT FORM FOR PARTICIPATION IN RESEARCH PROJECTS AND
CLINICAL TRIALS**

Principal Investigator: Dr L. Pollard BSc MSc MRCP
 King's College Hospital
 Denmark Hill
 London
 SE5 9RS

**Title of Project: Standards Of Care For People With Inflammatory Arthritis:
 Establishing A Local Framework To Deliver National Standards - Defining
 Medical Perspectives.**

Name of Researcher: Dr L. Pollard BSc MSc MRCP

Please initial box

1. I confirm that I have read and understand the information sheet dated July 17th, 2006 (version 1) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, ☐
3. I agree to take part in the above study. ☐

 Name of Patient

 Date

 Signature

 Researcher

 Date

 Signature

Appendix 4: Health professionals focus group interview schedule

INTERVIEW SCHEDULE (Health Care Professionals)

There are two main themes to be discussed in the focus group, firstly what information you feel should be collected during the routine care of patients with rheumatoid arthritis and secondly, to define the optimal interaction of the multidisciplinary team as well as between primary and secondary care.

At the end I would welcome any further information you may feel is relevant to the multidisciplinary care provided to patients with rheumatoid arthritis and also your thoughts on taking part in the study. The focus groups will last for approximately one hour but can go on longer if needed. The discussion will be recorded on tape and can be paused at any time. If you provide any information you do not wish to have recorded, the tape recorder can be stopped at any time and restarted at your request.

Outpatient Assessment

1. What questions do you routinely ask a patient with RA when you see them in your clinic?
 - eg pain and fatigue levels, general questions about arthritis
 - eg Difficulty at work/home
 - eg Other general health questions
2. What questions do feel we should be asking routinely?
3. What information do you give out routinely to patients with RA?
 - eg Benefits available
 - eg Help in getting back to work if appropriate
 - eg self- management
4. What assessments do you currently undertake when you see a patient with RA?
 - eg Joint assessments, pain and fatigue assessments
 - eg Examine feet
 - eg General examination
 - eg BP
 - eg Cardiovascular risk factor assessments
5. What assessments do you think should be done in a routine appointment?

Interaction between Primary and Secondary Care

1. What do you think is the role of the rheumatologist in the care of patients with RA?
 - eg Regular follow-ups
 - eg Prescribing and monitoring of drugs
 - eg Coordinating care across multidisciplinary team

2. What do you think is the role of the General Practitioner in the care of patients with RA?

- eg Prescribing and monitoring of drugs
- eg Monitoring of cardiovascular risk factors
- eg Help with social support

3. How can we improve the interaction between primary and secondary care to improve the care provided for patients with RA?

- eg Shared care record, electronic/paper form held by patient

Interaction of the Multidisciplinary Team

1. What do you think are the role of the allied health professionals and when should their care be accessed by patients with RA?

- eg OT, Physio, Podiatry
- eg Rheumatology nurse specialists
- eg on diagnosis, regular sessions

2. How can we improve the access and referral to allied professionals for patients with RA?

- eg Primary or secondary care referrals
- eg community or hospital care

Appendix 5: ARMA standards of care in inflammatory arthritis audit tool



PATIENT QUESTIONNAIRE INFLAMMATORY ARTHRITIS ARMA STANDARDS OF CARE SURVEY

You have been given this questionnaire because you have a type of Inflammatory Arthritis (for example, Rheumatoid Arthritis is an inflammatory arthritis). It is important to hear your views about the service you receive.

We would like to see whether people are receiving care as set out in the national Standards of Care published by ARMA (Arthritis & Musculoskeletal Alliance). These standards were developed by patients and health professionals to provide guidelines as to what care patients should receive.

Your help in filling in this questionnaire will help us to improve services for people with arthritis. The information you provide will not be identified to you and **is confidential**. There are no right or wrong answers. Just complete the form as truthfully as possible based upon your own experience in receiving care.

Please complete **one** box only, **unless** the question asks you to tick more than one box. If you would like to add any additional comments, they can be added at the end of this form in the spaces provided or on an additional blank sheet.

Any text should be written in **BLOCK CAPITALS**.

If you would like a copy of the published Standards of Care, please ask your Rheumatologist or Rheumatology nurse.

Patient Questionnaire – Inflammatory Arthritis
ARMA Standards of Care Survey

Name and Town of the HOSPITAL you are attending _____

A: YOUR DIAGNOSIS

1. What type of arthritis do you have and how long have you been diagnosed?

	Less than 2 years	More than 2 years
Rheumatoid Arthritis	<input type="checkbox"/>	<input type="checkbox"/>
Psoriatic Arthritis	<input type="checkbox"/>	<input type="checkbox"/>
Ankylosing Spondylitis	<input type="checkbox"/>	<input type="checkbox"/>
Juvenile Idiopathic Arthritis (Arthritis started in childhood)	<input type="checkbox"/>	<input type="checkbox"/>
Don't Know	<input type="checkbox"/>	<input type="checkbox"/>
Other type of inflammatory arthritis (please specify) _____	<input type="checkbox"/>	<input type="checkbox"/>

2. Your age today _____

B: SMOKING & Exercise

1. Are you a ☐ Current Smoker ☐ Ex-smoker ☐ Never smoked
(Please tick one box. If ex-smoker or never smoked, please go to **Question 3**)
2. As a current smoker, have you ever been offered advice about how to give up by:
- | | | |
|--|--------------------------|--------------------------|
| | Yes | No |
| Your family doctor (GP)/practice nurse | <input type="checkbox"/> | <input type="checkbox"/> |
| A member of the Rheumatology Team* | <input type="checkbox"/> | <input type="checkbox"/> |
- *Rheumatology team = Rheumatologist/Rheumatology Doctor, Nurse Specialist, Occupational Therapist, Physiotherapist, Podiatrist
3. Have you been offered advice about exercise programmes run at (or recommended by) the hospital?
- | | | |
|--|--------------------------|--------------------------|
| | Yes | No |
| | <input type="checkbox"/> | <input type="checkbox"/> |

C: INFLAMMATORY ARTHRITIS

- | | Yes | No | Don't know |
|---|--------------------------|--------------------------|--------------------------|
| 1. Did you know or think you had an arthritis-related condition before you first visited your GP? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. At this visit, did your GP advise you to take a painkiller or offer advice about how to control your pain? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

D: EARLY DIAGNOSIS AND TREATMENT

1. How many of the following people did you see about your arthritis within the first six months of your diagnosis? (tick all that apply)

☐ Rheumatologist ☐ Nurse Specialist ☐ Podiatrist
☐ Physiotherapist ☐ Occupational Therapist ☐ Dietician
☐ Other (please specify) _____

2. When you were first diagnosed, were you offered any of the following medications?
(Tick all that apply. If unsure, please ask a member of the department to explain.)

☐ Disease Modifying medication
(e.g. Methotrexate, suphasalazine, etc.)

☐ Anti-inflammatory
(e.g. Brufen, Lodine)

☐ Painkiller
(e.g. paracetamol)

☐ Steroid Tablet

☐ Steroid Injection

☐ Don't Know

- | 3. | Within six months of diagnosis, were you offered/given: | Yes | No |
|----|--|------------------------------|-----------------------------|
| | Teaching/education sessions about your disease and treatments? | <input type="checkbox"/> | <input type="checkbox"/> |
| | Written information about your disease and treatments? | <input type="checkbox"/> | <input type="checkbox"/> |
| | Details of organisations to contact for further information and support? | <input type="checkbox"/> | <input type="checkbox"/> |
| | Information on how to contact the NHS Expert Patient Programme? | <input type="checkbox"/> | <input type="checkbox"/> |
| | Information about continuing employment/education or returning to work? N/A <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | Information about benefits? N/A <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | Information about continuing your interests and leisure activities? | <input type="checkbox"/> | <input type="checkbox"/> |
| | A helpline number in case you need help, advice or support between outpatient visits? | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. | Are you given the opportunity to discuss ongoing concerns at visits? | Yes <input type="checkbox"/> | No <input type="checkbox"/> |

E: YOUR TREATMENT

- | | Yes | No |
|--|--------------------------|--------------------------|
| 1. Have you been involved in decisions about your treatment? | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Have you ever been given a written plan about your care? | <input type="checkbox"/> | <input type="checkbox"/> |

**Patient Questionnaire – Inflammatory Arthritis
ARMA Standards of Care Survey**

- | | Yes | No |
|--|--------------------------|--------------------------|
| 3. Have you been asked to provide feedback of the service / care you have received so far? | <input type="checkbox"/> | <input type="checkbox"/> |

F: ONGOING TREATMENT AND SUPPORT

- | | Yes | No | Don't know |
|--|--------------------------|--------------------------|--------------------------|
| 1. Have you been advised to contact your rheumatology team if your arthritis flares / becomes worse? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

2. Between rheumatology outpatient visits, does your GP / Practice Nurse check or ask you about the following:

<i>Heart Disease</i>	Always	Sometimes	Never
a) Blood pressure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b) Cholesterol levels	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c) Smoking status	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d) Weight	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e) Any shortness of breath / chest pain / cough	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>General Health</i>			
f) Any symptoms relating to your digestive system (e.g. bowels)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g) Blood tests	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h) Urine tests	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. How often is your arthritis assessed and reviewed by:

	Annually	More often	Less often	Never	Don't Know
Rheumatologist / Doctor	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nurse Specialist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Physiotherapist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Occupational Therapist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Podiatrist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dietician	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
GP / Practice Nurse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other (please specify)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Patient Questionnaire – Inflammatory Arthritis
ARMA Standards of Care Survey**

	Annually	More often	Less often	Never	Don't know
4. Are your interests / hobbies and emotional needs assessed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Is your pain assessed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Have you had support in managing your pain? <i>(If Yes, tick all that apply)</i>	Yes <input type="checkbox"/>	No <input type="checkbox"/>			
<input type="checkbox"/> Relaxation <input type="checkbox"/> Painkillers / Anti-inflammatories <input type="checkbox"/> Practical advice					
<input type="checkbox"/> Other(s) (please specify) _____					
G. Are there any additional comments you would like to add about your Multi-disciplinary Team? (Multidisciplinary team = Rheumatology Team, GP and Practice Nurse)					

Please return to:

THANK YOU FOR YOUR TIME

Appendix 6: Tjhuis patient satisfaction questionnaire**SATISFACTION QUESTIONNAIRE**

Thinking of the care you have received in the rheumatology department at King's College Hospital, please indicate how much you agree with the following statements by circling the appropriate answer.

	Totally Disagree	Disagree	Neither Agree nor Disagree	Agree	Totally Agree
The care providers did not know what each other was doing	0	1	2	3	4
While under care, I found the quality of the different facilities such as the waiting room the surgery and the treatment room was good	0	1	2	3	4
In such a devastating disease as RA, the care providers could have shown more understanding	0	1	2	3	4
I was kept well informed about the reasons of investigations and care	0	1	2	3	4
The care had a favourable effect on my RA	0	1	2	3	4
It was difficult to reach the care providers	0	1	2	3	4
In general, per group of care providers (eg occupational therapists or physiotherapists), I was treated by the same carer	0	1	2	3	4
The information I received about RA and its treatment was clear	0	1	2	3	4
After the start of treatment, it took a lot of time before the different care providers could see me.	0	1	2	3	4
I underwent investigations and treatments that appeared irrelevant	0	1	2	3	4
There was not much information available about RA and its treatment.	0	1	2	3	4

	Totally Disagree	Disagree	Neither Agree nor Disagree	Agree	Totally Agree
I had the impression that the care providers knew a great deal about RA	0	1	2	3	4
The care providers respected my own wishes and ideas concerning the care	0	1	2	3	4
The end-results of the care were disappointing	0	1	2	3	4
The care providers were perceptive of what having RA means to me	0	1	2	3	4
Per group of care providers (eg physiotherapists or rheumatologists), I was treated by many different carers	0	1	2	3	4
The information I received about RA was difficult to understand	0	1	2	3	4
The carers provided a lot of verbal information about RA and its treatment.	0	1	2	3	4
The treatment rooms and other facilities that were used during my care could have been much better.	0	1	2	3	4
The collaboration among the care providers was good.	0	1	2	3	4
The care was quick and good; No inappropriate investigations or treatments were performed	0	1	2	3	4
After referral by the rheumatologist, the care started promptly	0	1	2	3	4
There was always someone to confer with if I had problems or questions	0	1	2	3	4
During the care, I was seen promptly by different care providers	0	1	2	3	4
The care providers knew little about RA	0	1	2	3	4

	Totally Disagree	Disagree	Neither Agree nor Disagree	Agree	Totally Agree
The care providers decided which treatment was the best for me; I could not influence this decision	0	1	2	3	4
A considerable amount of time elapsed between the referral by the rheumatologist and the commencement of other treatments	0	1	2	3	4
I was repeatedly surprised; I was not informed about what was going on with regard to investigations and care	0	1	2	3	4

Appendix 7: Hill patient satisfaction questionnaire

PATIENT SATISFACTION QUESTIONNAIRE

**Rheumatism Research Unit
University of Leeds**

SATISFACTION WITH CARE

This questionnaire has been devised to tell us about your overall opinion of your care in the rheumatology out-patients clinic. It is not a test and there are no right or wrong answers. We are interested in your opinions and impressions, whether they are **GOOD** or **BAD**.

The questionnaire consists of a number of statements about your care in the clinic. Some statements may look the same but they are different so please read each one very carefully before filling it in.

Please place a tick in the column which resembles your opinions most closely.

ONLY TICK ONE BOX FOR EACH STATEMENT

The example below will show you how

	Strongly Agree	Agree	Not sure	Disagree	Strongly Disagree
The seats in the waiting area are very comfortable				✓	
There are always a lot of people attending the clinic		✓			

Please keep in mind that what we are trying to find out are **YOUR** opinions and not those of your husband, wife or neighbour, so please complete the questionnaire by yourself.

Please try to think about the care that you are receiving at the **PRESENT TIME** and give us your opinions about that.

THANK YOU FOR YOUR HELP

	Strongly agree	Agree	Not sure	Disagree	Strongly disagree
They don't seem to listen to anything I tell them during my consultation					
I feel that I'm in good hands when I come to the clinic					
The person I see in clinic takes an interest in my family					
I'm always given a clean explanation of why I am having tests done.					
There are some things about my care in the clinic which could be improved.					
I'm told everything I want to know about my arthritis drugs.					
During my consultation I'm given little or no medical explanation about my arthritis.					
Side effects of tablets are rarely discussed during my consultation.					
The person I see in clinic really knows what he/she is talking about.					
Visiting the clinic is not a stressful occasion.					
I am given good advice on how to cope with my arthritis.					
No matter how long you have to wait in clinic, it's worth it.					

	Strongly agree	Agree	Not sure	Disagree	Strongly disagree
I'm satisfied with the care I receive in the clinic.					
There's no one to get in touch with at the clinic if I have a problem.					
I'm rarely told why I need tests such as bloods and x-rays.					
My questions are answered in words that I find hard to understand.					
I find it difficult to talk about things that concern me when I'm in the clinic.					
The person I see in clinic has no interest in the effect my disease has on my family.					
It's easy to get an appointment if I need to come back to the clinic.					
I'm given as much time as I need for my consultation.					
The person I see in clinic sometimes appears uncertain about what they are doing.					
The person I see in the clinic is not as thorough as he/she should be.					
I am given very little information on how to cope with my arthritis.					
The person I see in clinic doesn't understand what its like to have arthritis.					

	Strongly agree	Agree	Not sure	Disagree	Strongly disagree
The person I see in clinic seems to know how it feels to have arthritis.					
I feel that I'm treated as a person rather than a disease.					
I've no confidence in the person who is treating me.					
I am encouraged to ask questions about my arthritis.					
If I had a problem it would be difficult to get someone to speak to over the phone.					
I'm rarely asked which treatments I would prefer.					
If I had a problem with my arthritis I would find it easy to get advice over the phone.					
My feelings about my treatment are taken into consideration.					
If I had a medical problem I feel sure it would be checked out when I came to the clinic.					
Prescriptions for new tablets are given without any explanation.					
I'm usually told what the possible side effects of the tablets could be.					
I'm encouraged to contact the person I see in clinic if I have a problem with my arthritis.					

	Strongly agree	Agree	Not sure	Disagree	Strongly disagree
The care I receive in the clinic is just about perfect.					
I hardly ever see the same person when I come for my appointment.					
The person I see in clinic appears skilful at their job.					
The person I see in clinic does not always talk sense.					
Sometimes the person I see in clinic is too busy to spend enough time with me.					
When I attend the clinic I'm told everything I want to know about my arthritis.					
It's hard to get an appointment if I need it quickly.					
I see the same person nearly every time I come to clinic.					
I'm usually kept waiting a long time in the waiting area.					

Appendix 8: Patient support group survey

**KING'S COLLEGE HOSPITAL
DEPARTMENT OF RHEUMATOLOGY**

ARE YOU INTERESTED IN A PATIENT SUPPORT GROUP?

Some patients have expressed an interest in forming a patient support group, and as this would be a 'new' development we are interested in your views.

A patient support group is organised and managed by patients. Support could be given from staff to help set up the initial meeting, but the how the group develops would be totally dependant on what its members wanted. Staff could also be called upon to deliver short talks or demonstrations, but the main idea is that it is run by you, the patients.

It would be helpful if you could take the time to answer the following questions, to give us an idea if there is a real need for such a group.

Please tick the appropriate answers and thank you for your time.

Do you think a patient support group is a good idea?

YES ☐ NO ☐

If there were to be a patient support group, would you attend?

YES ☐ NO ☐

IF YES:

How often do you feel it should meet?

Once a Month ☐ Every 3 Months ☐ Other (please specify)..... ☐

What time of day do you feel is the best time to hold a group?

Morning ☐ Afternoon ☐ Evening ☐

Where do you feel the group should be held?

King's College Hospital ☐ Elsewhere in the community ☐

Would you be interested in helping to set up and run such a group?

YES ☐ NO ☐

Once again, thank you for your time and views.

Appendix 9: SF-36 Questionnaire**THE SHORT FORM 36 HEALTH SURVEY QUESTIONNAIRE (SF-36)**

The following questions ask for your views about your health, how you feel and how well you are able to do your usual activities. If you are unsure about how to answer any questions please give the best answer you can and make any of your own comments if you like. Do not spend too much time in answering as your immediate response is likely to be the most accurate.

1. In general, would you say your health is:

*(Please tick **one** box)*

- | | |
|-----------|--------------------------|
| Excellent | <input type="checkbox"/> |
| Very good | <input type="checkbox"/> |
| Good | <input type="checkbox"/> |
| Fair | <input type="checkbox"/> |
| Poor | <input type="checkbox"/> |

2. Compared to one year ago, how would you rate your health in general **now**?

*(Please tick **one** box)*

- | | |
|---------------------------------------|--------------------------|
| Much better than one year ago | <input type="checkbox"/> |
| Somewhat better now than one year ago | <input type="checkbox"/> |
| About the same | <input type="checkbox"/> |
| Somewhat worse now than one year ago | <input type="checkbox"/> |
| Much worse now than one year ago | <input type="checkbox"/> |

3. Health and daily activities

The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

(Please tick **one** box on each line)

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports			
b) Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling or playing golf			
c) Lifting or carrying groceries			
d) Climbing several flights of stairs			
e) Climbing one flight of stairs			
f) Bending, kneeling or stooping			
g) Walking more than a mile			
h) Walking half a mile			
i) Walking 100 yards			
j) Bathing and dressing yourself			

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Answer **Yes** or **No** to each question)

	Yes	No
a) Cut down on the amount of time you spent on work or other activities		
b) Accomplished less than you would like		
c) Were limited in the kind of work or other activities		

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(Answer **Yes** or **No** to each question)

	Yes	No
a) Cut down on the amount of time you spent on work or other activities		
b) Accomplished less than you would like		
c) Didn't do work or other activities as carefully as usual		

6. How much **bodily pain** have you had during the **past 4 weeks**?

(Please tick **one** box)

Not at all	<input type="checkbox"/>
Slightly	<input type="checkbox"/>
Moderately	<input type="checkbox"/>
Quite a bit	<input type="checkbox"/>
Extremely	<input type="checkbox"/>

7. How much **bodily pain** have you had during the **past 4 weeks**?

(Please tick **one** box)

None	<input type="checkbox"/>
Very mild	<input type="checkbox"/>
Mild	<input type="checkbox"/>
Moderate	<input type="checkbox"/>
Severe	<input type="checkbox"/>
Very Severe	<input type="checkbox"/>

8. During the past 4 weeks how much did pain interfere with your normal work (including work both outside the home and housework)?

(Please tick **one** box)

Not at all	<input type="checkbox"/>
A little bit	<input type="checkbox"/>
Moderately	<input type="checkbox"/>
Quite a bit	<input type="checkbox"/>
Extremely	<input type="checkbox"/>

YOUR FEELINGS

These questions are about how you feel and how things have been with you **during the past month**. (For each question, please indicate the one answer that comes closest to the way you have been feeling).

9. How much time during **the last month**:

(Please tick **one** box on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?						
b. Have you been a very nervous person?						
c. Have you felt so down in the dumps that nothing could cheer you up?						
d. Have you felt calm and peaceful?						
e. Did you have a lot of energy?						
f. Have you felt downhearted and low?						
g. Did you feel worn out?						
h. Have you been a happy person?						
i. Did you feel tired?						
j. Has your health limited your social activities (like visiting friends or close relatives)?						

HEALTH IN GENERAL

10. Please choose the answer that best describes how **true** or **false** each of the following statements is for you.

(Please tick **one** box on each line)

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
a. I seem to get ill more easily than other people					
b. I am as healthy as anybody I know					
c. I expect my health to get worse					
d. My health is excellent					

Appendix 10: HAQ Questionnaire**HEALTH ASSESSMENT QUESTIONNAIRE (HAQ)**

PATIENT INITIALS

DATE OF ASSESSMENT

PATIENT STUDY NUMBER

We are interested in learning how your illness affects your ability to function in daily life.

Please feel free to add any comments at the end of this form.

Please tick one response which best describes your usual abilities over the past week

1. DRESSING and GROOMING	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
Are you able to:				
a. Dress yourself, including tying shoelaces and doing buttons?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. Shampoo your hair?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
2. RISING				
Are you able to:				
a. Stand up from an armless straight chair?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. Get in and out bed?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
3. EATING				
Are you able to:				
a. Cut your Meat?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. Lift a full cup or glass to your mouth?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
c. Open a new carton of milk (or soap powder)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
4. WALKING				
Are you able to:				
a. Walk outdoors on flat ground?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. Climb up five steps?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

Please tick any aids or devices that you usually use for any of these activities:

Cane ☐ Walking frame ☐ Built-up or special utensils ☐
 Crutches ☐ Wheelchair ☐ Special or built-up chair ☐
 Devices used for dressing ☐ Other (specify).....
 (buttonhooks, zipper pull, shoe horn)

Please tick any categories for which you usually need help from another person:

Dressing and Grooming ☐ Eating ☐
 Rising ☐ Walking ☐

Please tick the one response which best describes your usual abilities over the past week

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
5. HYGIENE				
Are you able to:				
a. Wash and dry your entire body?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. Take a bath?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
c. Get on and off the toilet?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
6. REACH				
Are you able to:				
a. Reach and get down a 5lb object (e.g. a bag of potatoes) from just above your head?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. Bend down to pick up clothing off the floor?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
7. GRIP				
Are you able to:				
a. Open car doors?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. Open jars which have been previously opened?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
c. Turn taps on and off?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
8. ACTIVITIES				
Are you able to:				
a. Run errands and shop?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. Get in and out of a car?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
c. Do chores such as vacuuming, housework or light gardening?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

Please tick any aids or devices that you usually use for any of these activities:

Raised toilet seat	<input type="checkbox"/>	Bath seat	<input type="checkbox"/>	Bath rail	<input type="checkbox"/>
Long handled appliances for reach	<input type="checkbox"/>	Jar opener (for jars previously opened)	<input type="checkbox"/>		<input type="checkbox"/>

Please tick any categories for which you usually need help from another person:

Hygiene	<input type="checkbox"/>	Gripping and opening things	<input type="checkbox"/>
Reach	<input type="checkbox"/>	Errands and housework	<input type="checkbox"/>

Appendix 11: FACIT-F questionnaire

FACIT-Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

		Not at all	A little bit	Some- what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired.....	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy.....	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An 12	I am too tired to eat.....	0	1	2	3	4
An 14	I need help doing my usual activities	0	1	2	3	4
An 15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An 16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 12: MAF Questionnaire

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE

Instructions: These questions are about fatigue and the effect of fatigue on your activities.

For each of the following questions, circle the number that most closely indicates how you have been feeling during the past week.

For example, suppose you really like to sleep late in the mornings. You would probably circle the number closer to the "a great deal" end of the line. This is where I put it:

Example: To what degree do you usually like to sleep late in the mornings?

Not at all A great deal

1. To what degree have you experienced fatigue?

Not at all A great deal

If no fatigue, stop here.

2. How severe is the fatigue which you have been experiencing?

Mild Severe

3. To what degree has fatigue caused you distress?

No distress A great deal
of distress

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE
(Continued)

Circle the number that most closely indicates to what degree fatigue has interfered with your ability to do the following activities in the past week. For activities you don't do, for reasons other than fatigue (e.g. you don't work because you are retired), check the box.

In the past week, to what degree has fatigue interfered with your ability to:

(NOTE: Check box to the left of each number if you don't do activity)

☐ **4. Do household chores**

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Not at all								A great deal	

☐ **5. Cook**

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Not at all								A great deal	

☐ **6. Bathe or wash**

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Not at all								A great deal	

☐ **7. Dress**

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Not at all								A great deal	

☐ **8. Work**

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Not at all								A great deal	

☐ **9. Visit or socialize with friends or family**

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
Not at all								A great deal	

(Continued)

(NOTE: Check box to the left of each number if you don't do activity)

☐ **10. Engage in sexual activity**

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
 Not at all A great deal

☐ 11. Engage in leisure and recreational activities

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
 Not at all A great deal

☐ **12. Shop and do errands**

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
 Not at all A great deal

13. Walk

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
 Not at all A great deal

☐ 14. Exercise, other than walking

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
 Not at all A great deal

15. Over the past week, how often have you been fatigued?

☐ 4 Every day
☐ 3 Most, but not all days
☐ 2 Occasionally, but not most days
☐ 1 Hardly any days

16. To what degree has your fatigue changed during the past week?

☐ 4 Increased
☐ 3 Fatigue has gone up and down
☐ 2 Stayed the same
☐ 1 Decreased

Appendix 13: MFSI Questionnaire

The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF)

Below is a list of statements that describe how people sometimes feel. Please read each item carefully, then circle the one number next to each item which best describes **how true each statement has been for you in the past seven days.**

Not at all	A little	Moderately	Quite a bit	Extremely
------------	----------	------------	-------------	-----------

1. I have trouble remembering things	0	1	2	3	4
2. My muscles ache	0	1	2	3	4
3. I feel upset	0	1	2	3	4
4. My legs feel weak	0	1	2	3	4
5. I feel cheerful	0	1	2	3	4
6. My head feels heavy	0	1	2	3	4
7. I feel lively	0	1	2	3	4
8. I feel nervous	0	1	2	3	4
9. I feel relaxed	0	1	2	3	4
10. I feel pooped	0	1	2	3	4
11. I am confused	0	1	2	3	4
12. I am worn out	0	1	2	3	4
13. I feel sad	0	1	2	3	4
14. I feel fatigued	0	1	2	3	4
15. I have trouble paying attention	0	1	2	3	4

Not at all	A little	Moderately	Quite a bit	Extremely
---------------	-------------	------------	----------------	-----------

16. My arms feel weak	0	1	2	3	4
17. I feel sluggish	0	1	2	3	4
18. I feel run down	0	1	2	3	4
19. I ache all over	0	1	2	3	4
20. I am unable to concentrate	0	1	2	3	4
21. I feel depressed	0	1	2	3	4
22. I feel refreshed	0	1	2	3	4
23. I feel tense	0	1	2	3	4
24. I feel energetic	0	1	2	3	4
25. I make more mistakes than usual	0	1	2	3	4
26. My body feels heavy all over	0	1	2	3	4
27. I am forgetful	0	1	2	3	4
28. I feel tired	0	1	2	3	4
29. I feel calm	0	1	2	3	4
30. I am distressed	0	1	2	3	4

Appendix 14: HADS Questionnaire

Hospital Anxiety and Depression Scale (HADS)

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

1. I feel tense or 'wound up':

Most of the time
A lot of the time
Time to time, occasionally
Not at all

2. I feel as if I am slowed down:

<input type="checkbox"/> Nearly all of the time	<input type="checkbox"/>
<input type="checkbox"/> Very often	<input type="checkbox"/>
<input type="checkbox"/> Sometimes	<input type="checkbox"/>
<input type="checkbox"/> Not at all	<input type="checkbox"/>

3. I still enjoy the things I used to enjoy:

Definitely as much
Not quite so much
Only a little
Not at all

4. I get a sort of frightened feeling like 'butterflies in the stomach':

<input type="checkbox"/> Not at all	<input type="checkbox"/>
<input type="checkbox"/> Occasionally	<input type="checkbox"/>
<input type="checkbox"/> Quite often	<input type="checkbox"/>
<input type="checkbox"/> Very often	<input type="checkbox"/>

5. I get a sort of frightened feeling like something awful is about to happen:

Very definitely and quite badly
Yes, but not too badly
A little, but it doesn't worry me
Not at all

6. I have lost interest in my appearance:

<input type="checkbox"/> Definitely	<input type="checkbox"/>
<input type="checkbox"/> I don't take as much care as I should	<input type="checkbox"/>
<input type="checkbox"/> I may not take quite as much care	<input type="checkbox"/>
<input type="checkbox"/> I take just as much care as ever	<input type="checkbox"/>

7. I can laugh and see the funny side of things:

As much as I always could
Not quite so much now
Definitely not so much now
Not at all

8. I feel restless as if I have to be on the move:

<input type="checkbox"/> Very much indeed	<input type="checkbox"/>
<input type="checkbox"/> Quite a lot	<input type="checkbox"/>
<input type="checkbox"/> Not very much	<input type="checkbox"/>
<input type="checkbox"/> Not at all	<input type="checkbox"/>

9. Worrying thoughts go through my mind:

A great deal of the time
A lot of the time
From time to time but not too often
Only occasionally

10. I look forward with enjoyment to things:

<input type="checkbox"/> As much as I ever did	<input type="checkbox"/>
<input type="checkbox"/> Rather less than I used to	<input type="checkbox"/>
<input type="checkbox"/> Definitely less than I used to	<input type="checkbox"/>
<input type="checkbox"/> Hardly at all	<input type="checkbox"/>

11. I feel cheerful:

Not at all
Not often
Sometimes
Most of the time

13. I can sit at ease and feel relaxed:

Definitely
Usually
Not often
Not at all

12. I get sudden feelings of panic:

<input type="checkbox"/>	Very often indeed	<input type="checkbox"/>
<input type="checkbox"/>	Quite often	<input type="checkbox"/>
<input type="checkbox"/>	Not very often	<input type="checkbox"/>
<input type="checkbox"/>	Not at all	<input type="checkbox"/>

14. I can enjoy a good book or radio or TV programme:

<input type="checkbox"/>	Often	<input type="checkbox"/>
<input type="checkbox"/>	Sometimes	<input type="checkbox"/>
<input type="checkbox"/>	Not often	<input type="checkbox"/>
<input type="checkbox"/>	Very seldom	<input type="checkbox"/>

Appendix 15: Fatigue questionnaire and pain study consent form**CONSENT FORM FOR PARTICIPATION IN RESEARCH PROJECTS AND
CLINICAL TRIALS**

Principal Investigator: Dr L. Pollard BSc MSc MRCP
 King's College Hospital
 Denmark Hill
 London
 SE5 9RS

**Title of Project: Identifying the Optimal Multidimensional Tool to Measure
 Fatigue in Rheumatoid Arthritis and its Potentially Reversible Causes.**

Name of Researcher: Dr L. Pollard MSc, MRCP

Please initial box

1. I confirm that I have read and understand the information sheet dated September 23rd, 2005 (version 0.3) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from King's College Hospital, and/or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

 Name of Patient

 Date

 Signature

 Researcher

 Date

 Signature